AFRICAN CENTERS OF EXCELLENCE IN BIOINFORMATICS

KAMPALA, UGANDA

Gene Regulatory Networks 1

Yunhua Zhu,
PhD. in stem cell biology

Computational Genomics Specialist – Transcriptomics

Bachelor in biochemistry @NUS
PhD in stem cell biology @NUS
Postdoc in neurodegeneration, single cell biology @JHU
Bioinformatician @ NIH

Recent projects
- Single cell analysis of cancer stem cells
- Single cell analysis of immune response in lung cancer
- Bulk RNA-seq on irradiation, HIV blood samples

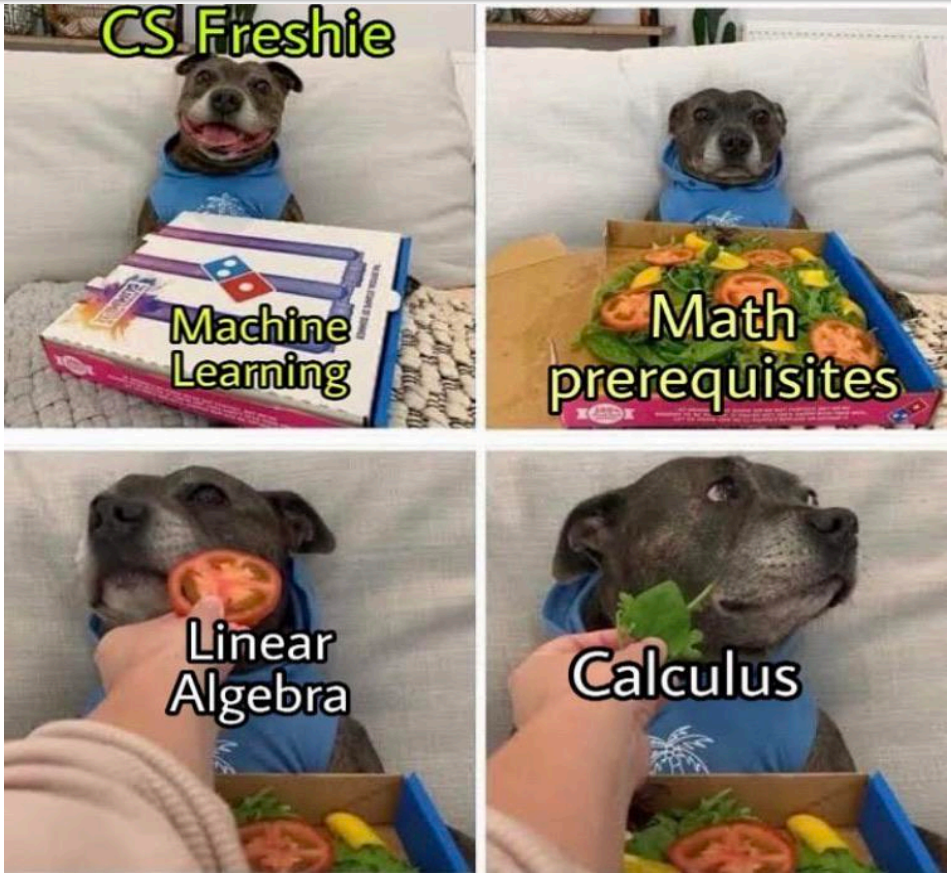
- PLEASE JOIN THE DISCUSSION

Today's Instructor

- Bioinformatics and Computational Biosciences Branch (BCBB), NIAID
- National Institutes of Health, Bethesda, MD USA.
- Contact our team via email:
  - GitHub: https://github.com/niaid/Gene_Regulatory_Networks
  - Instructors: zhuy16@nih.gov
  - Server: ssh username@137.63.194.9, /home/bcbb_teaching_files/
  - Googledoc, https://tinyurl.com/zhu-GRN
  - Email: bioinformatics@niaid.nih.gov
  - LinkedIn: https://tinyurl.com/zhu-linkedin

Personal experience: learning bioinformatics

- Sounds Nice
- A lot of difficulties
- Luckily…



B.Sc. and PhD in Biology
Postdoc training in neuroscience
Studied Single-cell RNA-seq

Key question today:
How to discovery regulatory connections and key players from a crowd of thousands of genes.

Biology in the modern era …

Microarray
RNA sequencing
Epigenomes
Single cell transcriptomics and Single cell Epigenomics
Microbiomes
Hard to digest
……

… What is my key factor to study?

The dog is FAAAT!!!

YouTube
Google
Wikipedia

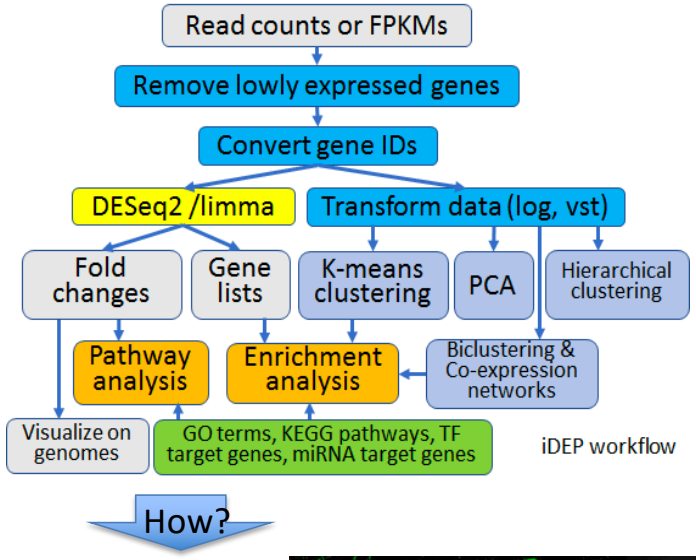
Statistics, Mathematics, Programming! All good stuff !!!

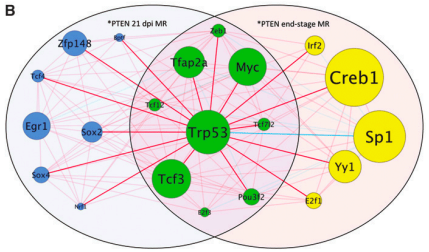
Objectives: achieve a general overview of GRN

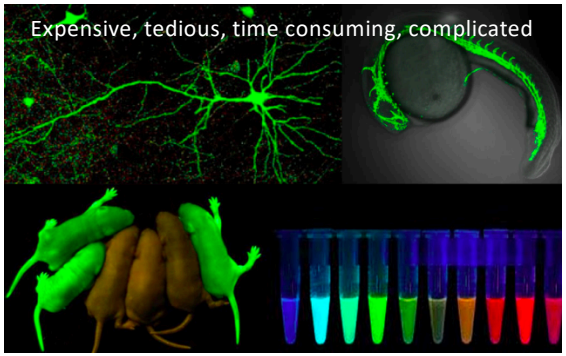
- Biological rational
- Theoretical bases of theories, intuitions and tools.
- Practical demonstration
- Links to further resources in case needed
- A discussion, not a lecture

Why study gene regulatory network

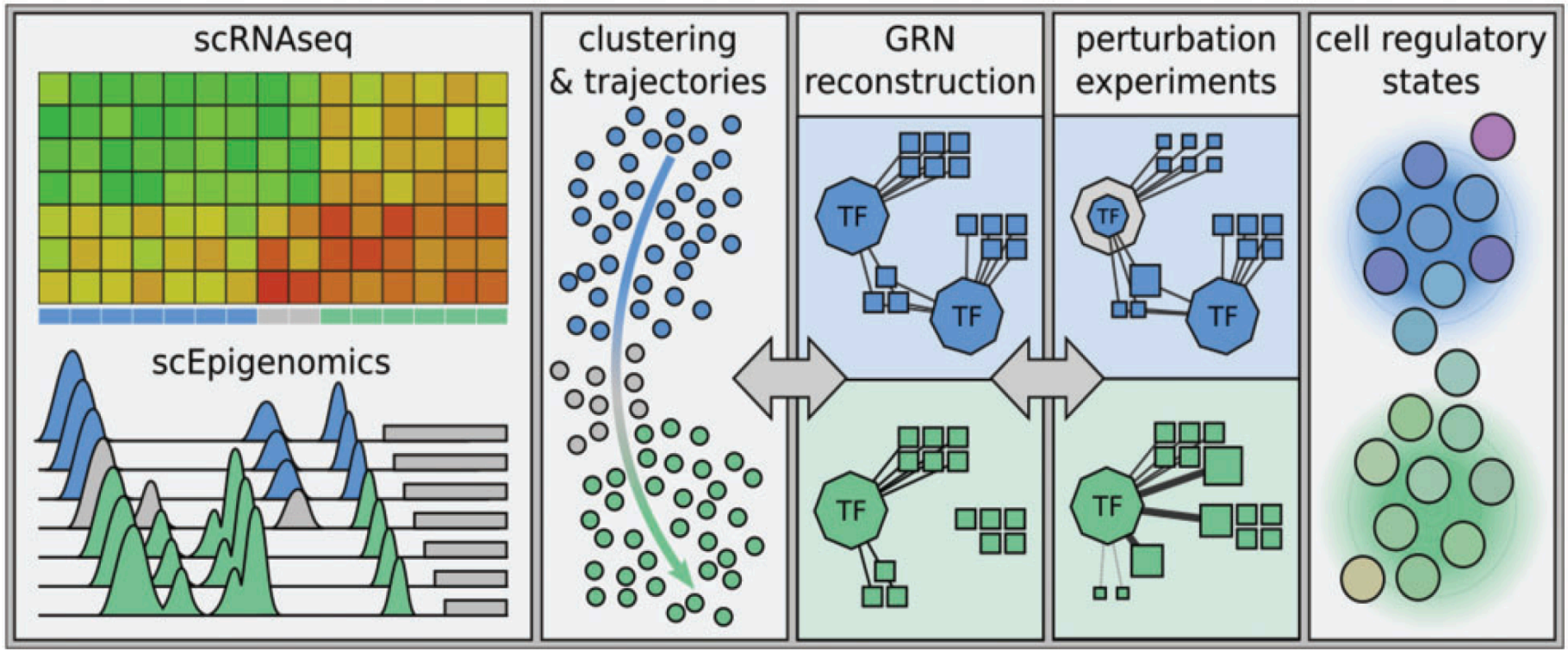
- Why
  - High throughput are screening procedures
  - Gene lists do not inform relationship between genes.
  - Regulatory information is hidden in the statistical relationships
  - Down-stream validation is costly, tediously and risky
- Aims
  - To find key candidate genes/master regulators for validation.
- Challenges
  - Data are massive, and mostly static that do not reflect dynamic regulation
  - Relationships can take various forms, linear or non-linear





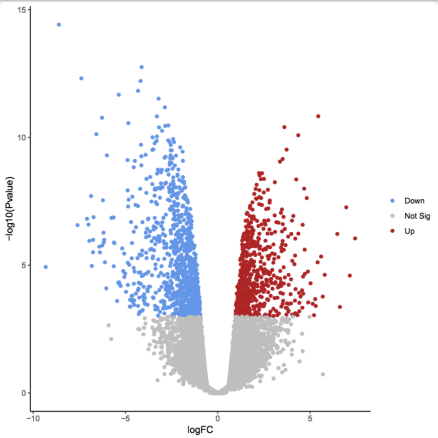


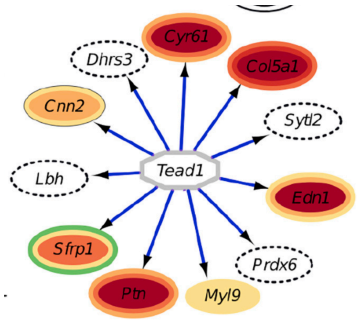
A workflow of a transcriptomic study

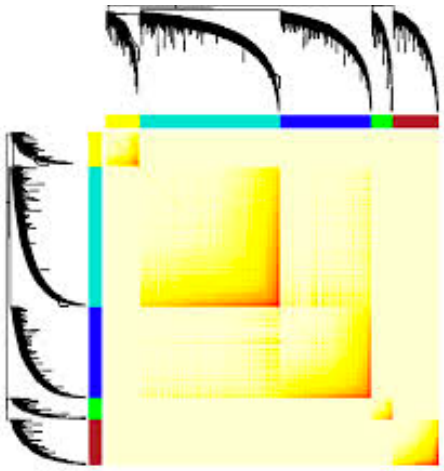


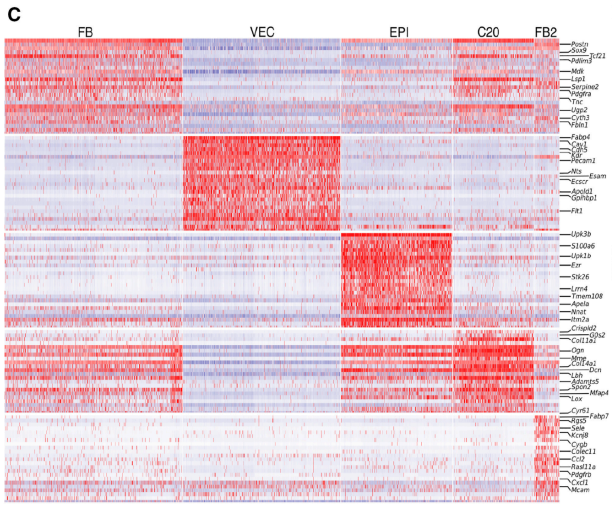
Prerequisite: identify a group of genes

- How to get a set of interesting genes?
  - Differential expression analysis
  - Clustering
  - WGCNA: Weighted Gene Co-expression Network Analysis
    - Dynamic tree cutting.



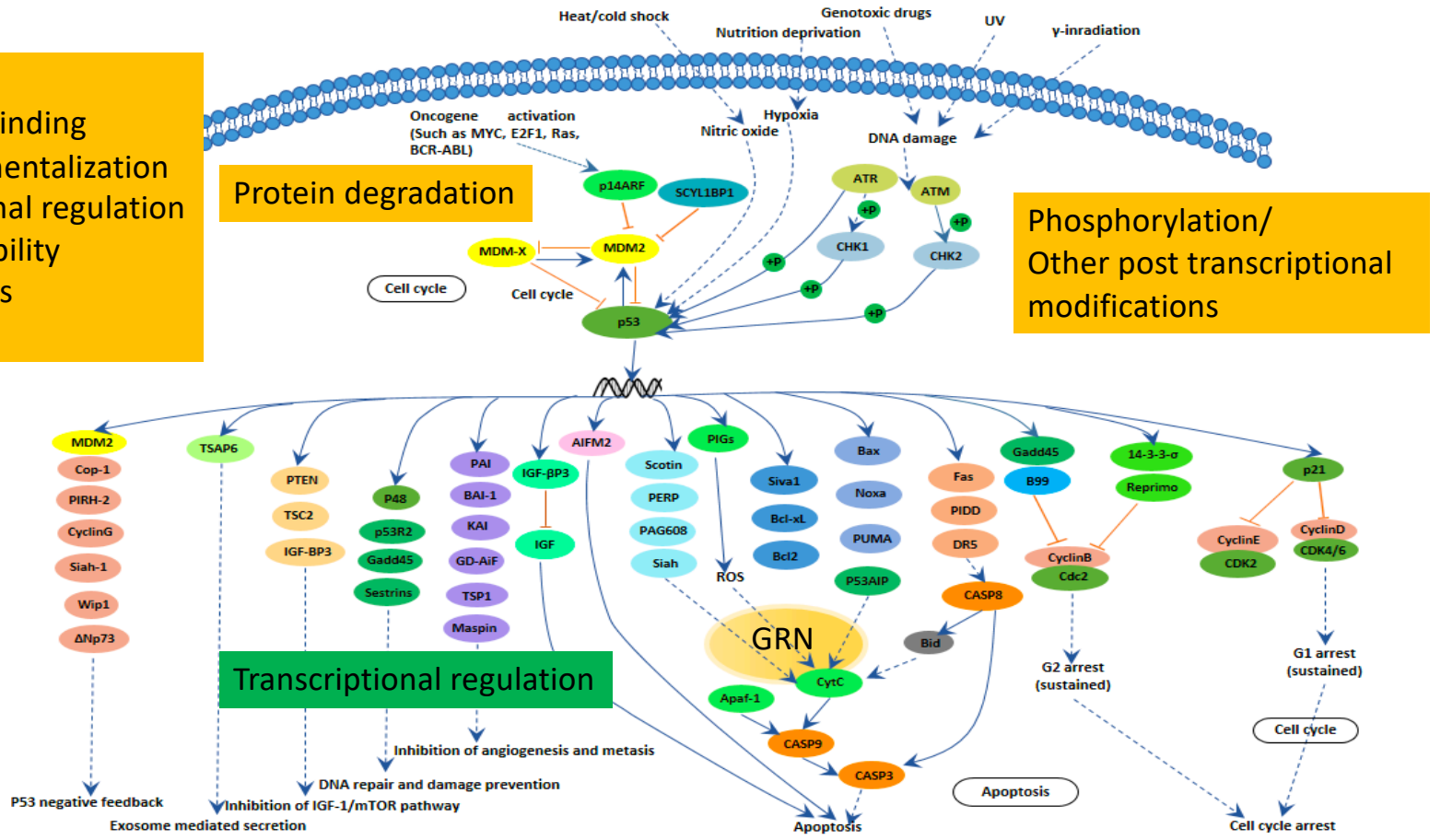






A side note: GRN is only a subset of cellular networks

Others
Cofactor binding
Compartmentalization
Translational regulation
mRNA stability
Epigenetics
...



A schematic illustration on the difference

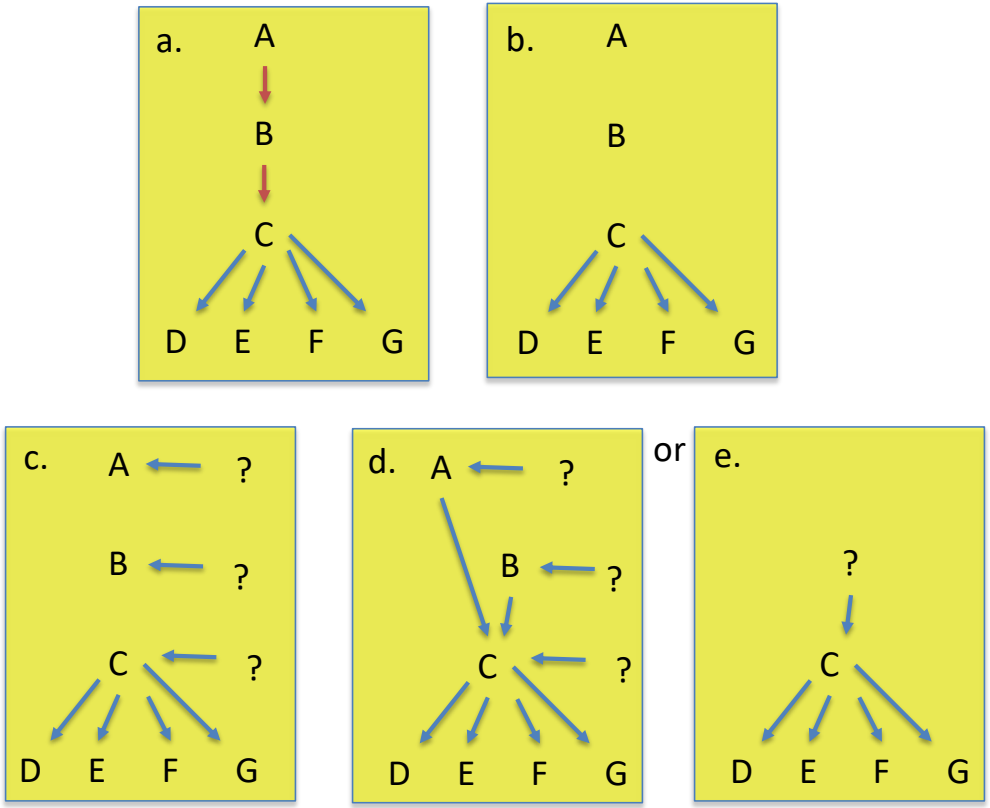
(a) conventional structure of intracellular signaling

(b) Biochemical link will be invisible in GRN

(c) Other regulators kick in

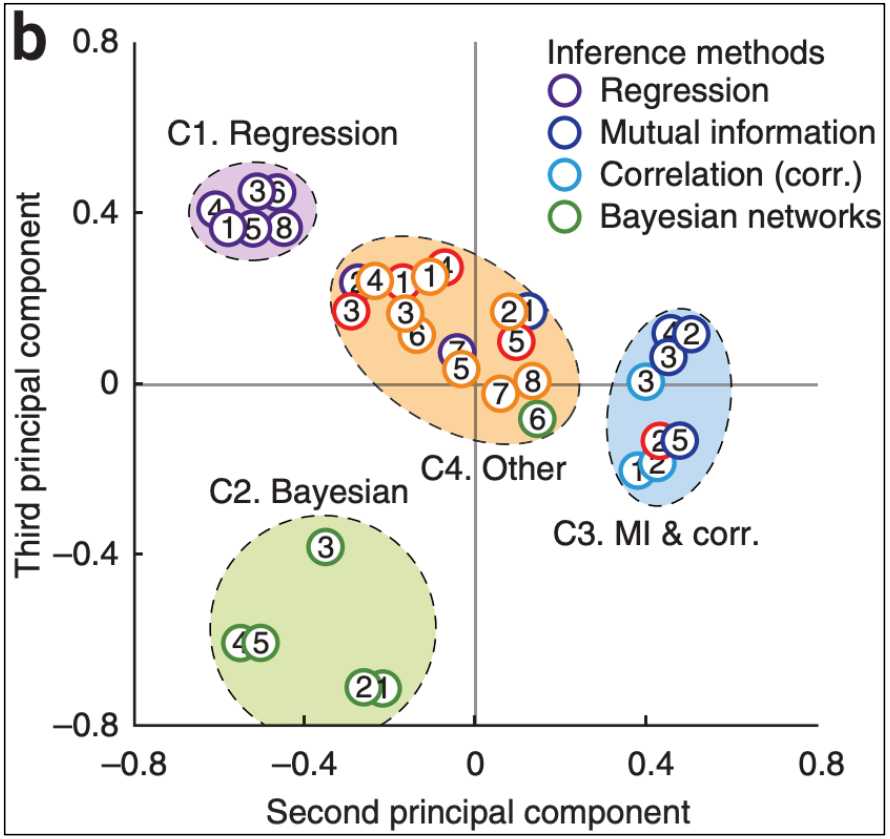
(d) Upstream factors may be independent from each other in the transcriptional GRN

(e) Upstream factors may be invisible



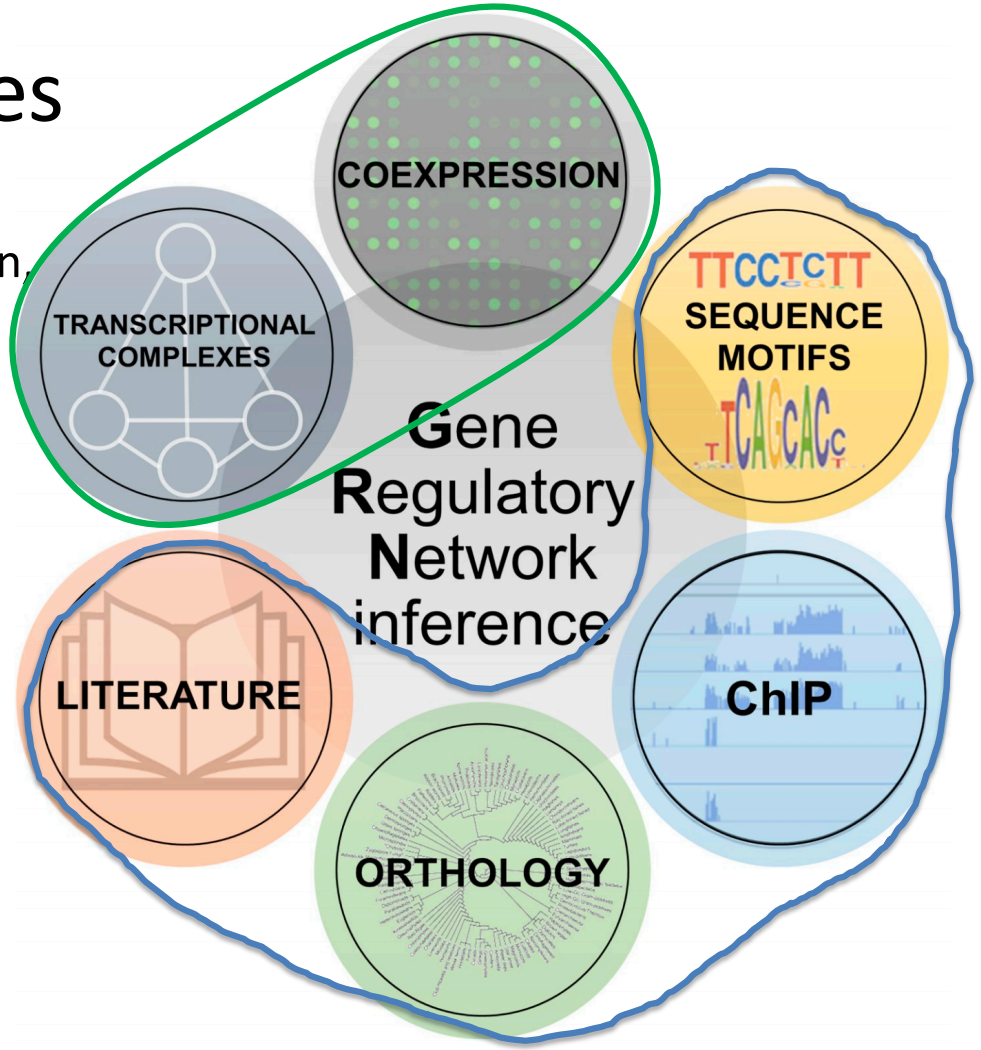
DREAM5– Network Inference Challenge (2010)

Dialogue for **R**everse **E**ngineering **A**ssessments and **M**ethods (Open science challenges)



Computational Strategies

- Infer network through expression pattern, based on linear/non-linear relationship between genes.
  - Linear relationships
  - Mutual information—linear/non-linear statistical relationships
  - Bayesian network /Bayes Net
  - Regression tree + random forest
- Predicting master regulators through promoter sequences
  - cis-Target and iRegulon
- Combinatory approach
  - SCENIC (GENIE3 and cis-Target)



Mercatelli et al., 2019

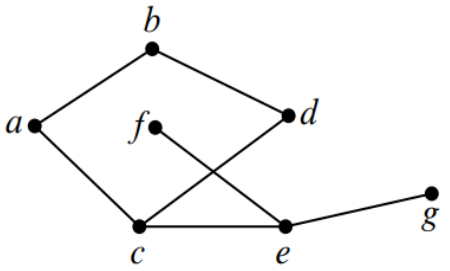
Overview of Tools in GRN inference

Software	ARACNE	NetworkInference/PIDC	bnlearn	GENIE3	iRegulon	SCENIC
semantics	Mutual information	Partial Information decomposition	Bayes theory	Random Forest, Regression tree	Promoter and TF binding sequence, database	Combination of regression and promoter sequence
years published	2006	2017	2009	2010	2014	2017
No. of cited	2179	82	894	658	337	265
FullName/ explanation	Algorithm for the Reconstruction of Accurate Cellular Networks	Using proportional unique contribution (PUC) to a target gene	Bayes net structure and parameter learning, causality	GEne Network Inference with Ensemble of trees	reverse-engineer the transcriptional regulatory network with regulatory sequence analysis	single-cell regulatory network inference and clustering
Implementation	GUI (geWorkbench)	Julia	R	R	GUI (Cytoscape)	R, Python
type of experiment	Microarray, bulk RNA-seq	Single cell data	General	single cell data	a list of gene names	single cell data
input format	csv	csv	csv	csv	a list	csv/loom file
output	network file	network file	directed network file	network file	network file/binding sequences	network file/heatmap

Graph/network theory: What are we estimating

- Graph (network) theory
  - Vertex (Vertices)/nodes
    - Genes
  - Edges
    - Undirected graph
      - ARACNE, PIDC
    - Directed Acyclic Graph (DAG)
      - Bayes net
    - Edge weights

Basic graph theory

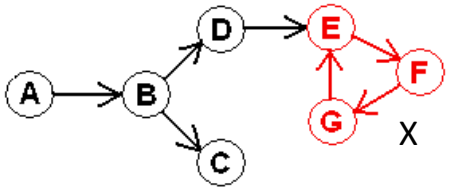


A undirected graph

The graph in Figure 5.1 is expressed mathematically as $G = (V, E)$, where:

$V = \{a, b, c, d, e, f, g, h, i\}$ Vertex/node

$E = \{\{a, b\}, \{a, c\}, \{b, d\}, \{c, d\}, \{c, e\}, \{e, f\}, \{e, g\}, \{h, i\}\}.$

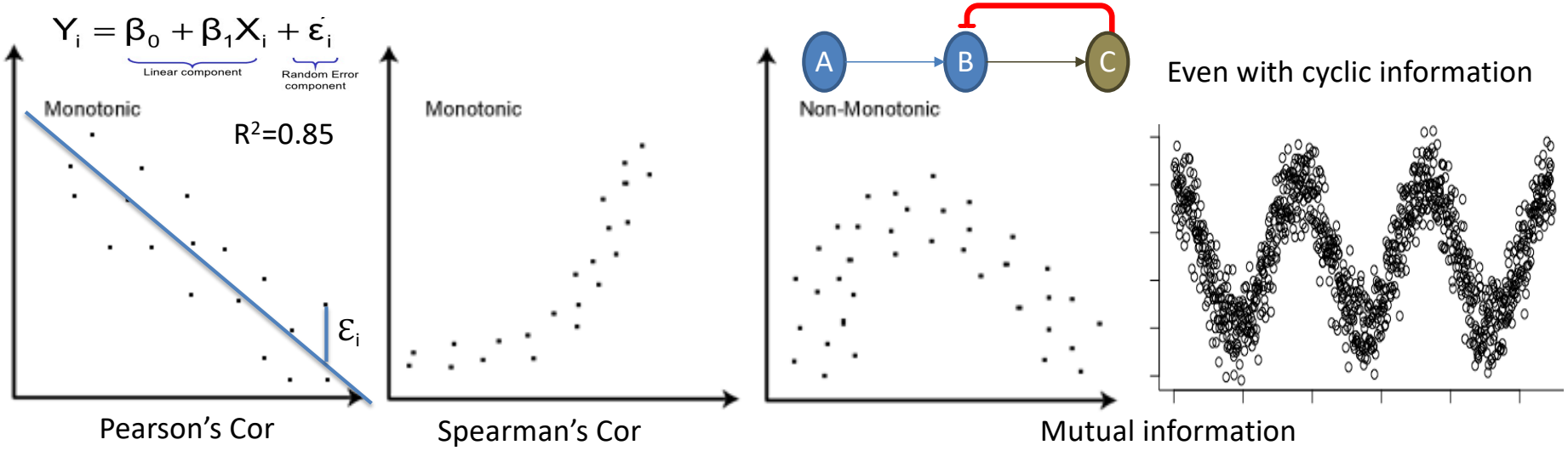


X

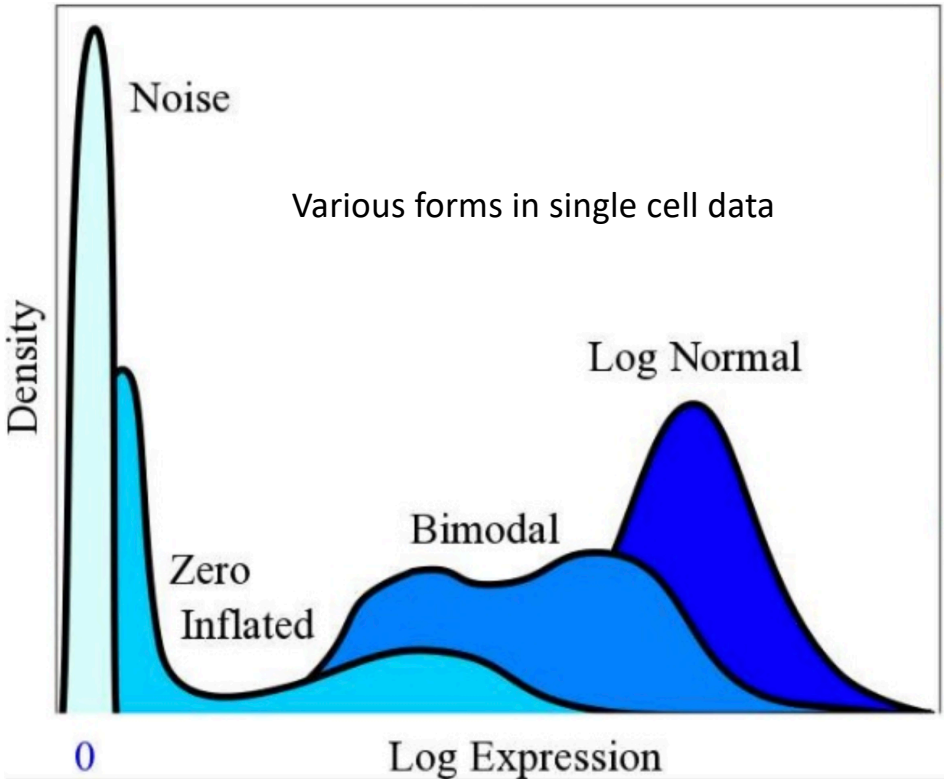
Directed Acyclic Graph (DAG)

Types of statistical relationship

- Pearson's correlation, low computational complexity, and their capability of inferring genome-wide networks even when a relatively low number of samples (*n* = 50) is available
- Spearman's correlation, rank based, no assumption on normal distribution
- Mutual information, any statistical relationship. But requires N to be sufficiently big for a good approximation.



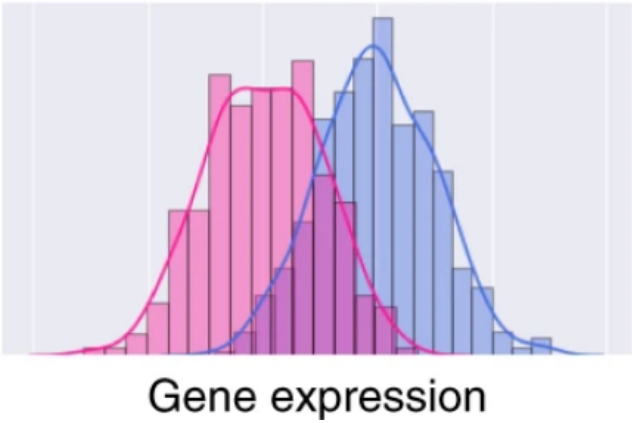
Various types of distributions of gene expression



Various forms in single cell data

https://www.slideshare.net/TimothyTickle/introduction-to-singlecell-rnaseq

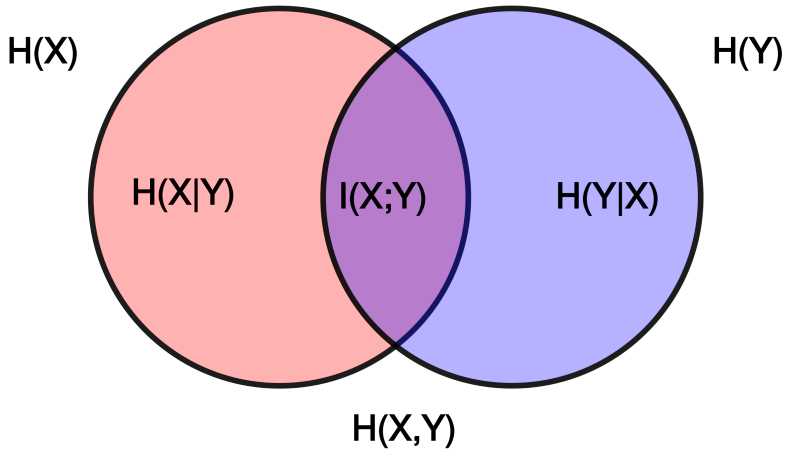
Two groups of cells
Log normal distribution



(Expression values of a gene in different samples /cells)

Information theory

- Entropy
  - Statistical information of a random variable can be calculated as Shannon's entropy
  - Statistical relationship (overlap) between two random variables can be calculated as mutual information



Shannon's Entropy—measure of information content. (Not the entropy in physics)

- Example:
  - **Gene1**
    - Probability of gene expression at 50 is 100% because all states average the same
  - **Gene2**
    - Probability of gene expressed at high level, 2/4=50%
    - at low level, 2/4=50%

$$H=\sum_{i=1}^{n} p_i \times \log_2\left(\frac{1}{p_i}\right)$$

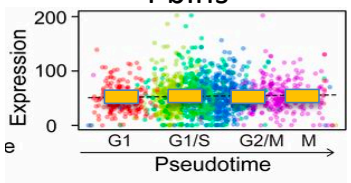
All the surprises your have got = entropy

How many times this event happen

That's why the unit is 'bits'.

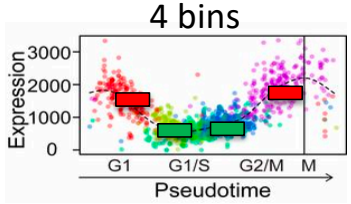
How surprise this event is. In another word, how rare is the event.

4 bins



H1=1/1x$\log_2$(1/1) + same + same +same=0 bits

4 bins



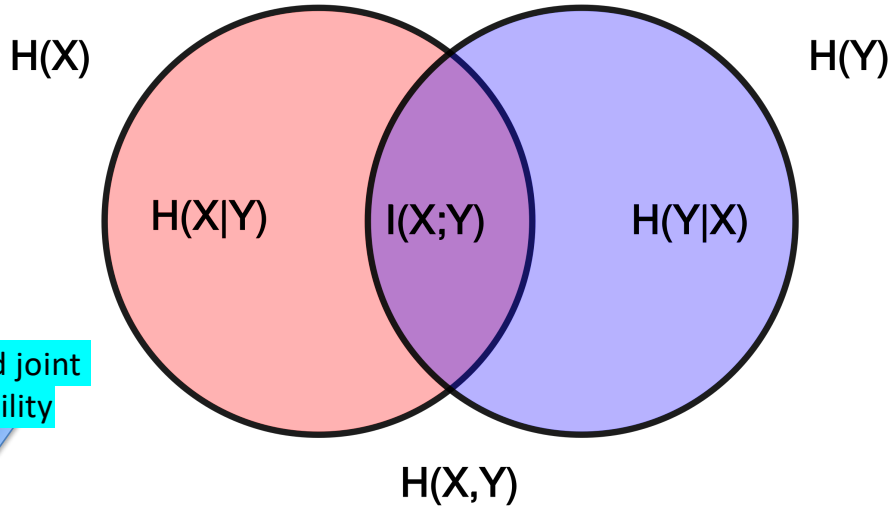
H2=1/(50%) x$\log_2$(1/50%) + 1/(50%) x$\log_2$(1/50%)+ same+ same=2x4=8 bits

PNAS Spatial transcriptome profiling by MERFISH reveals subcellular RNA

Method 1:
ARACNE

Mutual Information

- H(X), H(Y) are the information contents for X and Y
- I(X;Y) is the mutual information of X and Y



All the information your have got = entropy

Observed joint probability

Mutual information

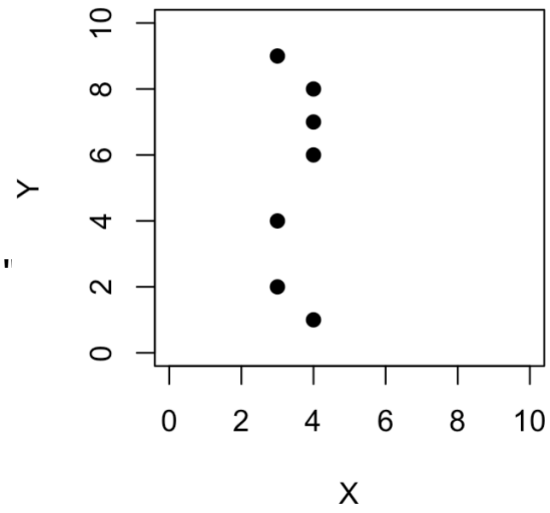
$$MI_{ij} = \sum_{x_i} \sum_{x_j} p(x_i, x_j) \log_2 \frac{p(x_i, x_j)}{p(x_i)p(x_j)}$$

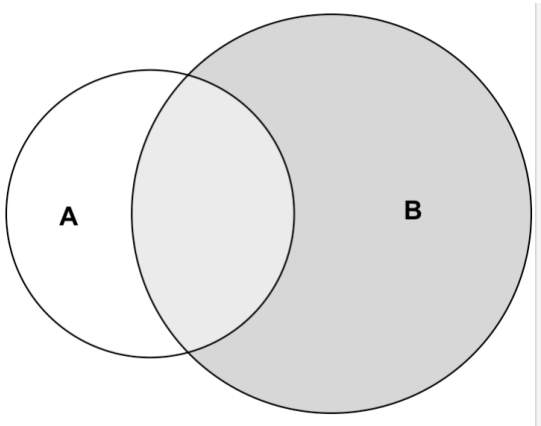
Equal to joint probability assuming x_i, x_j co-occur purely by chance.

An example

In R:

```
X=c(4,3,4,3,4,3,4)
Y=c(1,4,6,2,7,9,8)
plot(X,Y)
```






```
#install.packages("infotheo"
library(infotheo)
entropy(X)
entropy(Y)
mutinformation(X,Y)
#install.packages("eulerr")
library(eulerr)
fit <- euler(c(A = entropy(X), B = entropy(Y), "A&B" =
mutinformation(X,Y)))
plot(fit)
```

Breaking indirect connection: by DPI

Data processing inequality (DPI), to remove indirect interaction

$$x_i \rightarrow x_j \rightarrow x_k,$$

then,

$$I(x_i, x_k) \leq \min\left\{I(x_i, x_j), I(x_j, x_k)\right\}$$

If *i* and *k* are not directly connected, the correlation of them will not be high as a direct connection.

ARACNE workflow

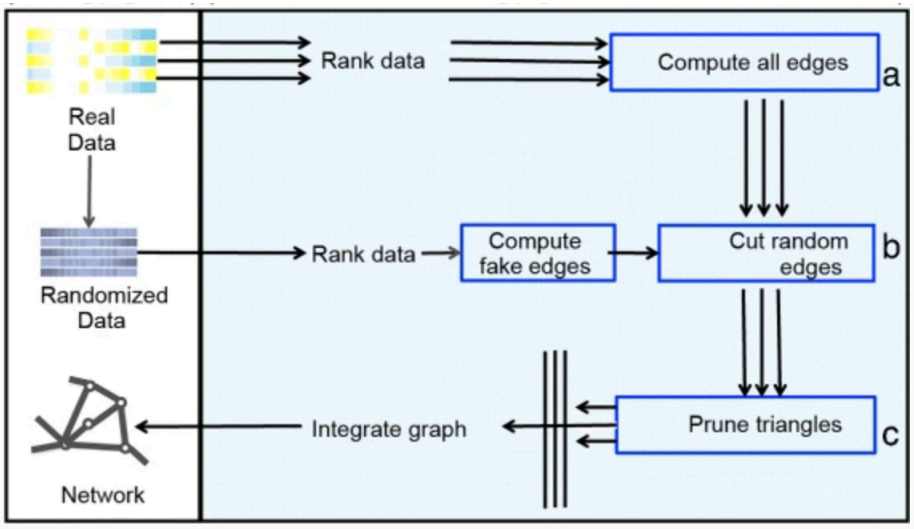


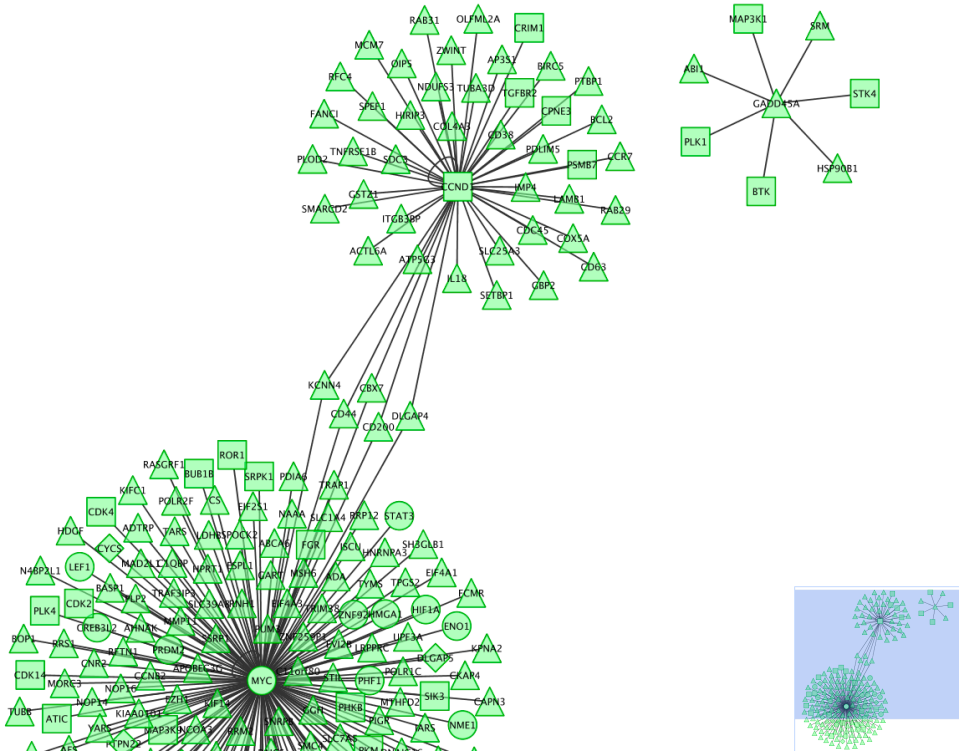
Illustration of how mutual information is calculated with 3 variables
https://www.youtube.com/watch?v=3iplfAfGzzI

Notes on running ARACNE

- geWorkbench will have ARACNE by default
  - http://wiki.c2b2.columbia.edu/workbench/index.php/Download_and_Installation
- What data to use for ARACNE
  - The Bcell-100.exp as an expression file
  - http://wiki.c2b2.columbia.edu/workbench/index.php/Tutorial_-_Data#Tutorial_data_files
  - Use HG_U95Av2.na36.annot.csv - most updated version
  - To download file need registration on Thermofisher website!!! Troublesome
- Video Tutorial: https://www.youtube.com/watch?v=CU4nukYswt0
- The layout of the geWorkbench is different from the video
  1. The project file cannot be created.
  2. The window looks different as well; no sub-division of windows at the bottom.

Demo ARACNE

- Using a microarray data
  - The interface of geWorkbench
  - setting parameters
  - Run ARACNE
  - Export from geWorkbench
  - Import to Cytoscape
  - Visualization



Discussion on ARACNE

- Good tool to find potential target genes with known TF
- Early and most widely used GRN software
- Straightforward concept of mutual information
- Processing inequality to break indirect linkages
- Too slow; newer implementation may be useful

Demonstration on ARACNE in geWorkbench

Bioinformatics. 2016 Jul 15;32(14):2233-5. doi: 10.1093/bioinformatics/btw216. Epub 2016 Apr 23.

ARACNe-AP: gene network reverse engineering through adaptive partitioning inference of mutual information.

Lachmann A[1], Giorgi FM[1], Lopez G[1], Califano A[1].

Author information

1 Department of Systems Biology, Columbia University, New York, NY, USA.

Abstract

The accurate reconstruction of gene regulatory networks from large scale molecular profile datasets represents one of the grand challenges of Systems Biology. The Algorithm for the Reconstruction of Accurate Cellular Networks (ARACNe) represents one of the most effective tools to accomplish this goal. However, the initial Fixed Bandwidth (FB) implementation is both inefficient and unable to deal with sample sets providing largely uneven coverage of the probability density space. Here, we present a completely new implementation of the algorithm, based on an Adaptive Partitioning strategy (AP) for estimating the Mutual Information. The new AP implementation (ARACNe-AP) achieves a dramatic improvement in computational performance (200× on average) over the previous methodology, while preserving the Mutual Information estimator and the Network inference accuracy of the original algorithm. Given that the previous version of ARACNe is extremely demanding, the new version of the algorithm will allow even researchers with modest computational resources to build complex regulatory networks from hundreds of gene expression profiles.

AVAILABILITY AND IMPLEMENTATION: A JAVA cross-platform command line ex
detailed usage guide are freely available on Sourceforge (http://sourceforge.net/

CONTACT: califano@c2b2.columbia.edu

SUPPLEMENTARY INFORMATION: Supplementary data are available at Bioinfo

https://github.com/califano-lab/ARACNe-AP

Bioinformatics. 2019 Jun 1;35(12):2165-2166. doi: 10.1093/bioinformatics/bty907.

SJARACNe: a scalable software tool for gene network reverse engineering from big data.

Khatamian A[1], Paull EO[2], Califano A[2], Yu J[1].

Author information

1 Department of Computational Biology, St. Jude Children's Research Hospital, Memphis, TN, USA.
2 Department of Systems Biology, Columbia University, New York, NY, USA.

Abstract

SUMMARY: Over the last two decades, we have observed an exponential increase in the number of generated array or sequencing-based transcriptomic profiles. Reverse engineering of biological networks from high-throughput gene expression profiles has been one of the grand challenges in systems biology. The Algorithm for the Reconstruction of Accurate Cellular Networks (ARACNe) represents one of the most effective and widely-used tools to address this challenge. However, existing ARACNe implementations do not efficiently process big input data with thousands of samples. Here we present an improved implementation of the algorithm, SJARACNe, to solve this big data problem, based on sophisticated software engineering. The new scalable SJARACNe package achieves a dramatic improvement in computational performance in both time and memory usage and implements new features while preserving the network inference accuracy of the original algorithm. Given that large-sampled transcriptomic data is increasingly available and ARACNe is extremely demanding for network reconstruction, the scalable SJARACNe will allow even researchers with modest computational resources to efficiently construct complex regulatory and signaling networks from thousands of gene expression profiles.

AVAILABILITY AND IMPLEMENTATION: SJARACNe is implemented in C++ (computational core) and Python (pipelining scripting wrapper, ≥3.6.1). It is freely available at https://github.com/jyyulab/SJARACNe.

SUPPLEMENTARY INFORMATION: Supplementary data are available at Bioinformatics online.

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2 Department of Systems Biology, Columbia University, New York, NY, USA.

Abstract

SUMMARY: Over the last two decades, we have observed an exponential increase in the number of generated array or sequencing-based transcriptomic profiles. Reverse engineering of biological networks from high-throughput gene expression profiles has been one of the grand challenges in systems biology. The Algorithm for the Reconstruction of Accurate Cellular Networks (ARACNe) represents one of the most effective and widely-used tools to address this challenge. However, existing ARACNe implementations do not efficiently process big input data with thousands of samples. Here we present an improved implementation of the algorithm, SJARACNe, to solve this big data problem, based on sophisticated software engineering. The new scalable SJARACNe package achieves a dramatic improvement in computational performance in both time and memory usage and implements new features while preserving the network inference accuracy of the original algorithm. Given that large-sampled transcriptomic data is increasingly available and ARACNe is extremely demanding for network reconstruction, the scalable SJARACNe will allow even researchers with modest computational resources to efficiently construct complex regulatory and signaling networks from thousands of gene expression profiles.

AVAILABILITY AND IMPLEMENTATION: SJARACNe is implemented in C++ (computational core) and Python (pipelining scripting wrapper, ≥3.6.1). It is freely available at https://github.com/jyyulab/SJARACNe.

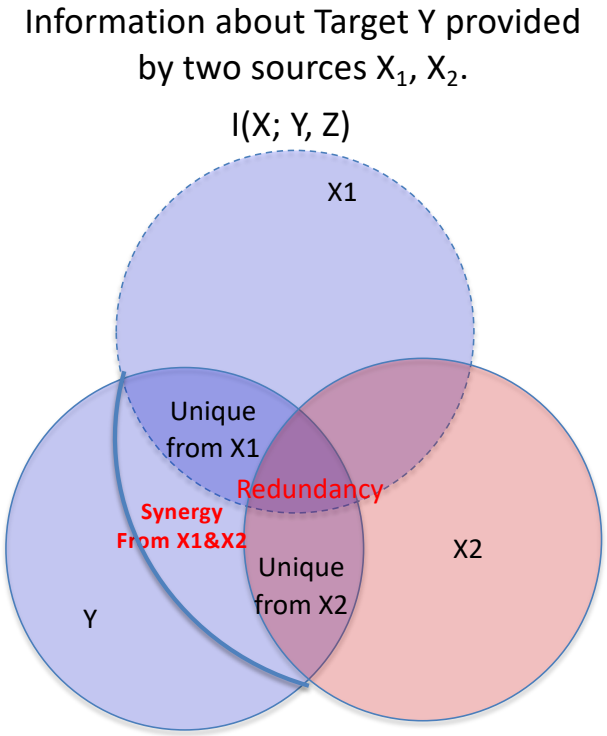
SUPPLEMENTARY INFORMATION: Supplementary data are available at Bioinformatics online.

https://github.com/califano-lab/ARACNe-AP

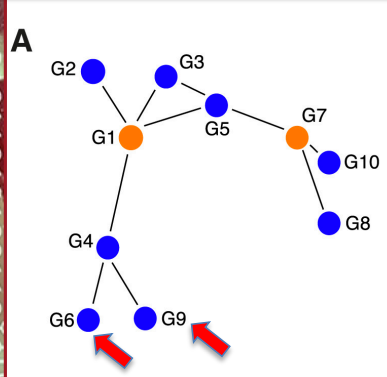
Method 2:
Partial Information Decomposition

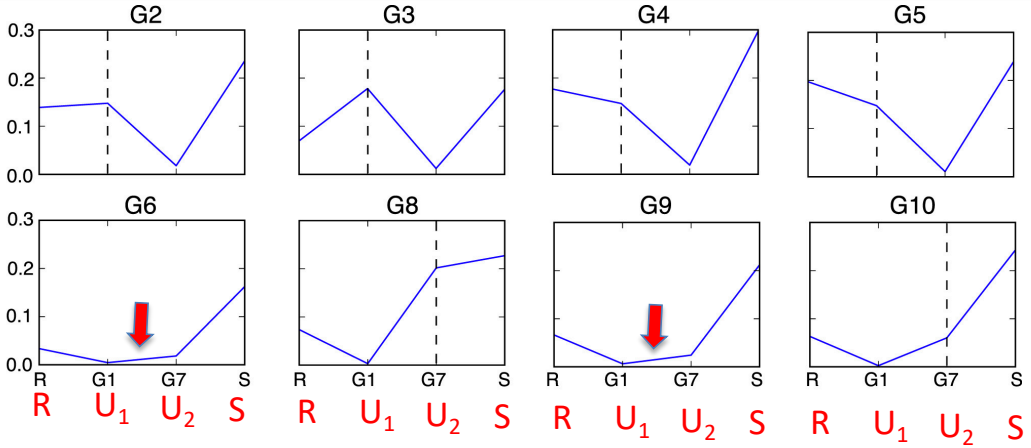
Information theory 2: Partial Information Decomposition

- Consider three variables X_1, X_2 and Y
- Consider that Y is dependent on X_1, X_2
- The information from X_1 and X_2 that matches Y can be decomposed to 4 components (Ux_1, Ux_2, Redundancy and Synergy)

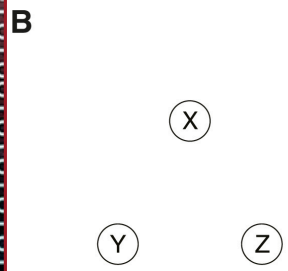


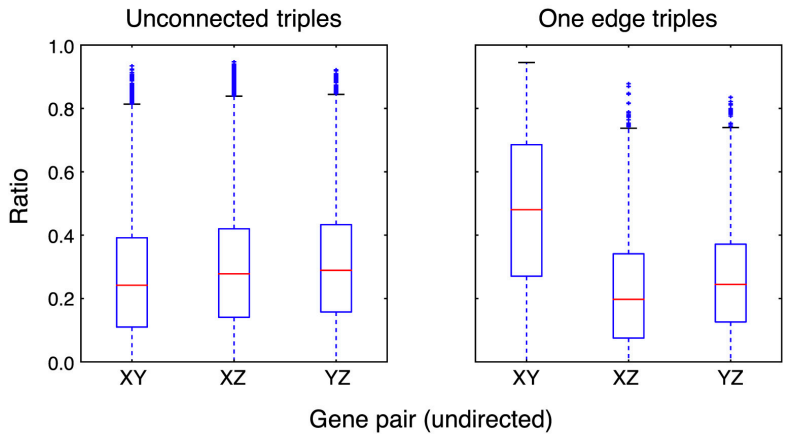
Are any of these components an indicator of a network connection?

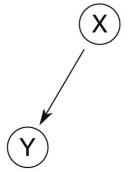


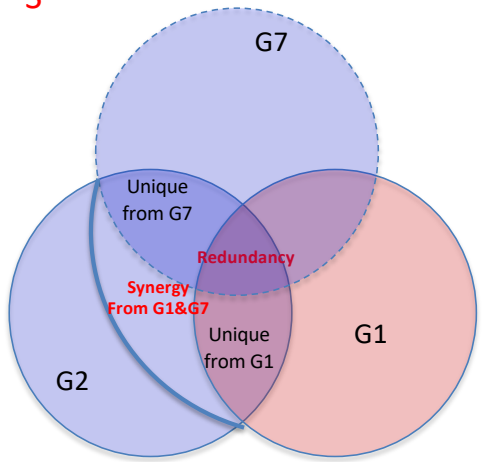


Yes, Unique information is most sensitive to a direct connection



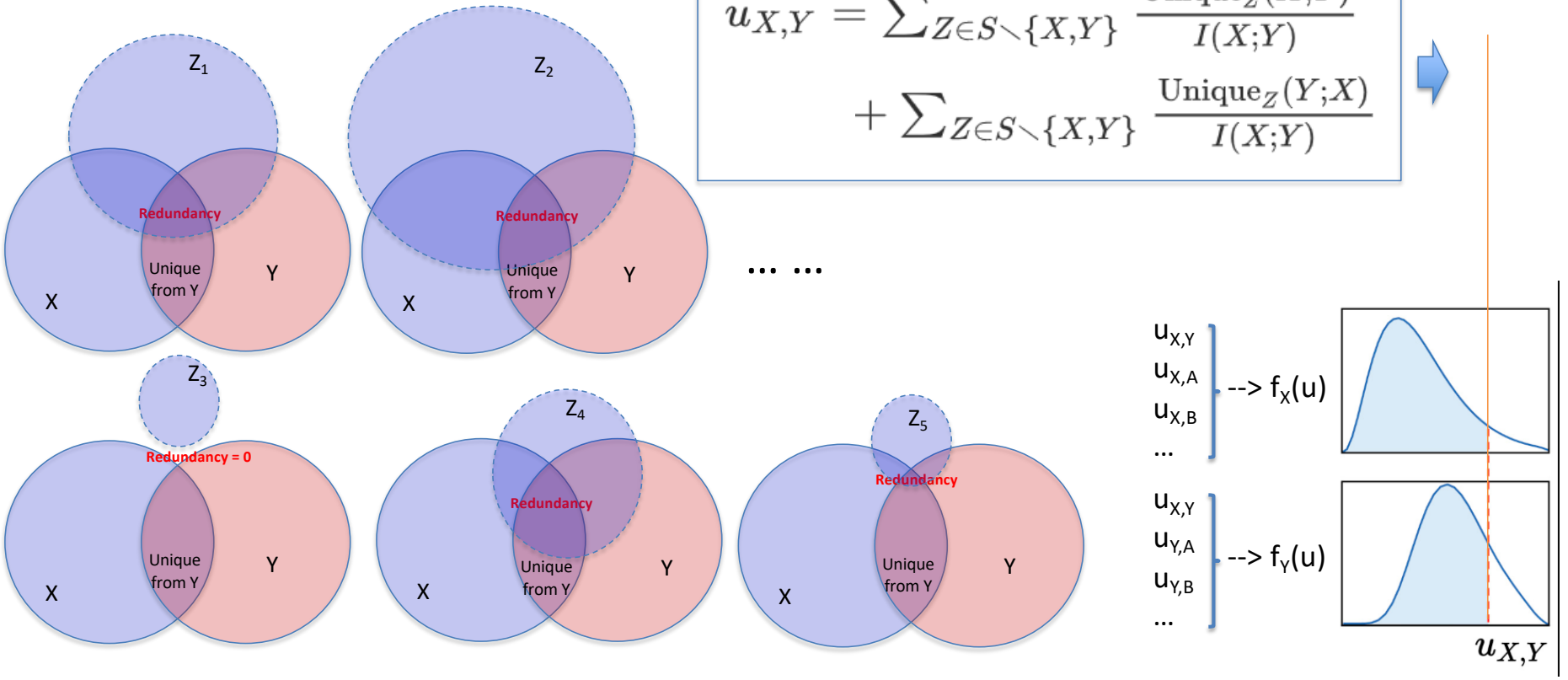






Proportional Unique Contribution

$$u_{X,Y} = \sum_{Z \in S \setminus \{X,Y\}} \frac{\text{Unique}_Z(X;Y)}{I(X;Y)} + \sum_{Z \in S \setminus \{X,Y\}} \frac{\text{Unique}_Z(Y;X)}{I(X;Y)}$$

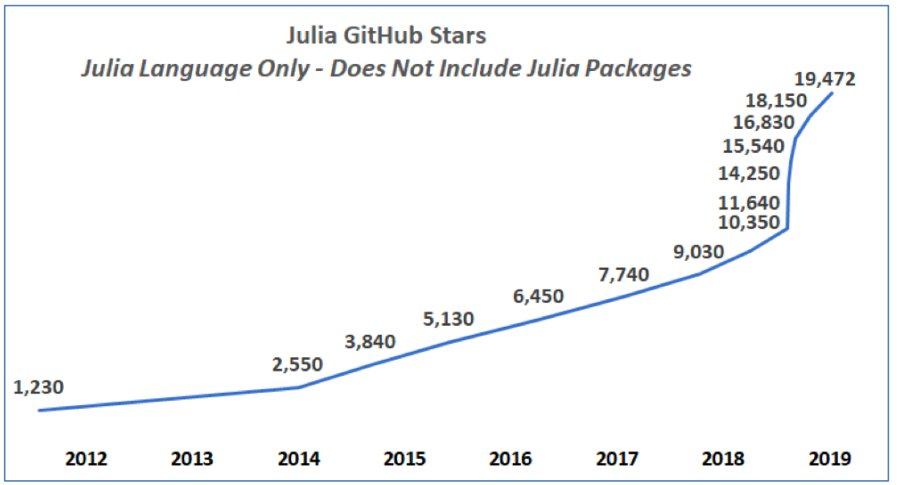


Discussion on NetworkInference

- Good at discovery of single edges, may systematically loose dense connections
- Relatively new, not sufficiently validated
- Easy to use in Julia, may need HPC to run large data
- Undirected, and no attempt is made to find the directionality of a regulation

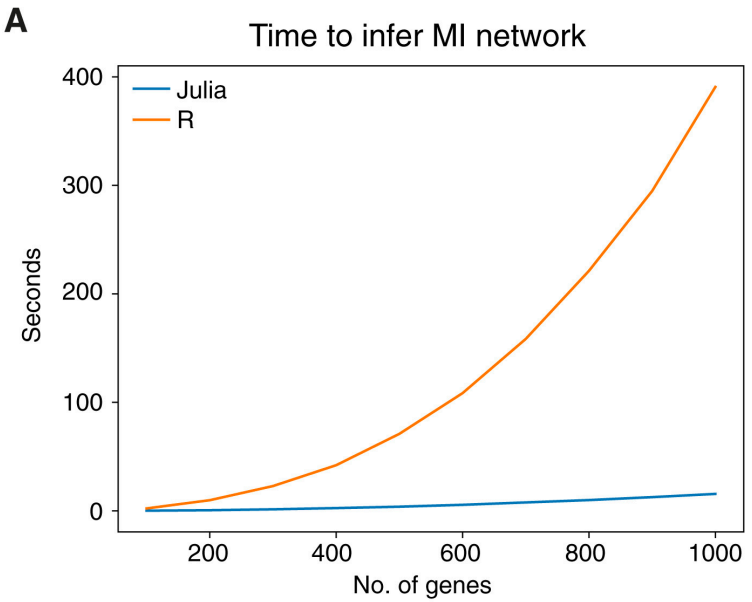
Julia: A fresh approach to numerical computing

- A young language developed by researchers in MIT on 2012
- Advantage, speed of C and intuitive as python
- Use all the libraries developed for python
- Disadvantage: updates a lot, as versions upgrade – not very stable



Implementation in Julia

- Using NetworkInference in Julia
  - Install Julia
    - https://julialang.org/downloads/, download the binary file for Generic Linux 64-bit
  - Install NetworkInference
  - Run examples

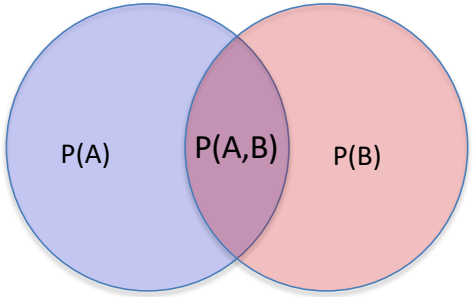


Demonstration on NetworkInference in Julia

- Import data
  - Run NetworkInference
  - Parameters
  - Export to CSV files
  - Import to Cytoscape for visulization

Method 3:

Bayesian Network – conditional dependence



P(A,B)=P(A|B)*P(B)=P(B|A)*P(A)

Bayes rule:

$$P(A \mid B) = \frac{P(B \mid A)P(A)}{P(B)}$$

Bayesian network – the conditional probability

If A and B are independent
A= winter (yes 25%, no 75%)
B= happy (yes 50%, no 50%)

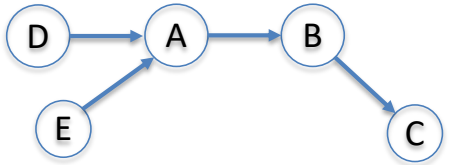
P(A) = 25%
P(B) = 50%
P(winter, happy) =
P(A,B)=25%*50%=12.5%
Correct

How about if B dependent on A:
A= winter (yes 25% or no 75%)
B= cold weather (overall yes 25%, no 75%)

P(A)=25%
P(B|A)=100% on winter and 0% on other seasons.
Overall 25%
The conditional probability of winter & cold is
P(A=winter, B=cold)=P(A)P(B)=25%*25%=6.25%
wrong!

P(winter, cold) =
P(A=winter;B=cold)=P(A)**P(B|A)**=25%*100%=25%

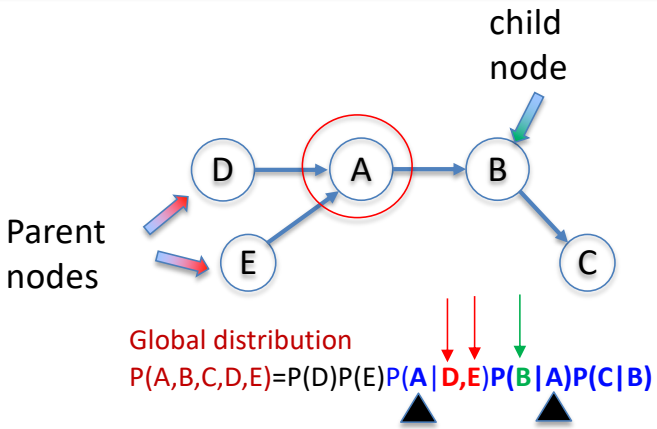
A= winter (yes or no 50% each)
B= cold weather (yes or no 100%)
C= wear sweater (yes or no, 50%)
D= month of a year
E= location on the earth



Global distribution
P(A,B,C,D,E)=P(D)P(E)P(A|D,E)**P(B|A)P(C|B)**

Parent nodes and child node

- To a given node
  - Conditional nodes (reasons or contributing factors) are called parents.
  - The consequent nodes are child nodes.



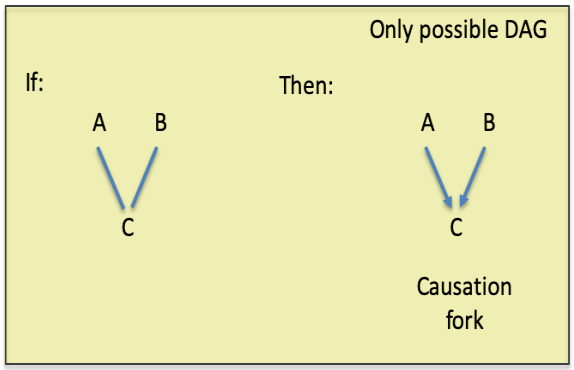
Assign directions: Induction of Causality algorithm

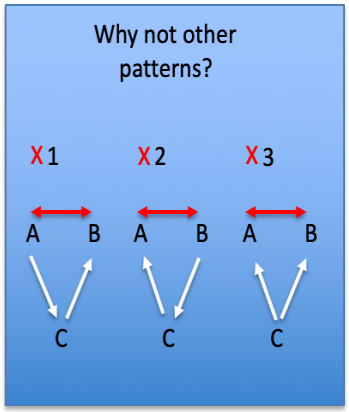
The Induction of Causality Algorithm:
If,

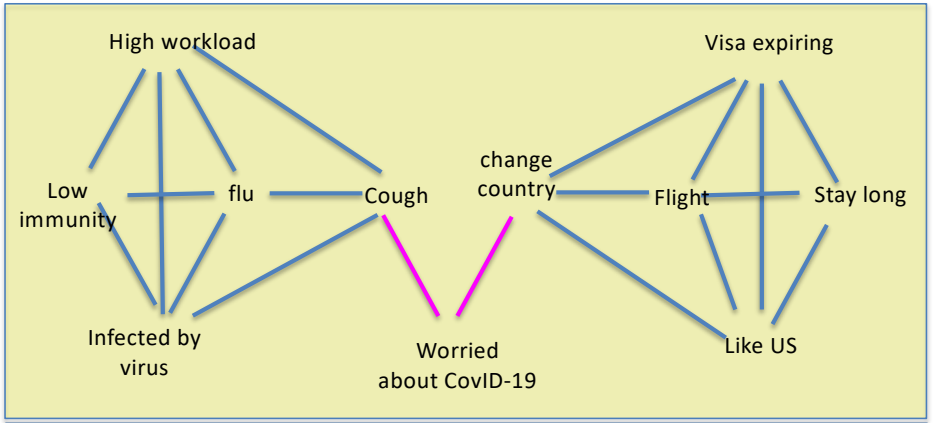
1. A, B are not connected through any other connection.
2. A and B have a common connection to C

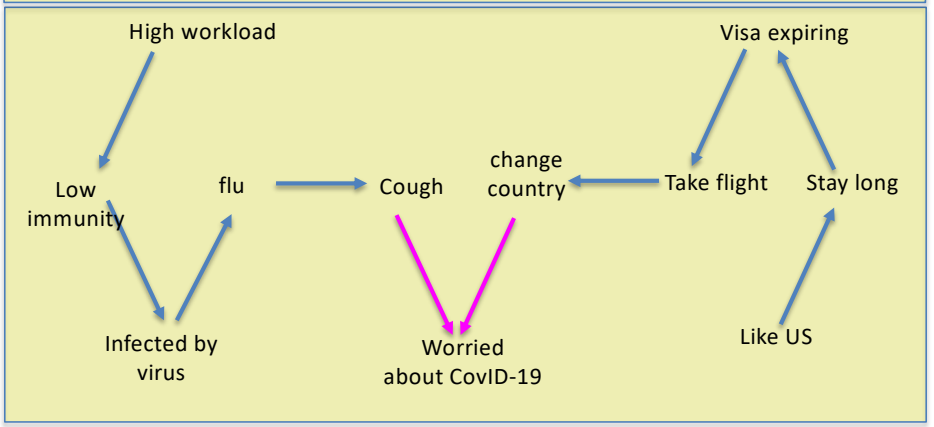
Then:

arrows point from A and B to C









Learn the network structure and parameters

Divide the Bayes net into two components:

- Θ: the conditional probabilities
- G: the structure
  - Can be decomposed to each node with parents (X_i and Π_{xi}).

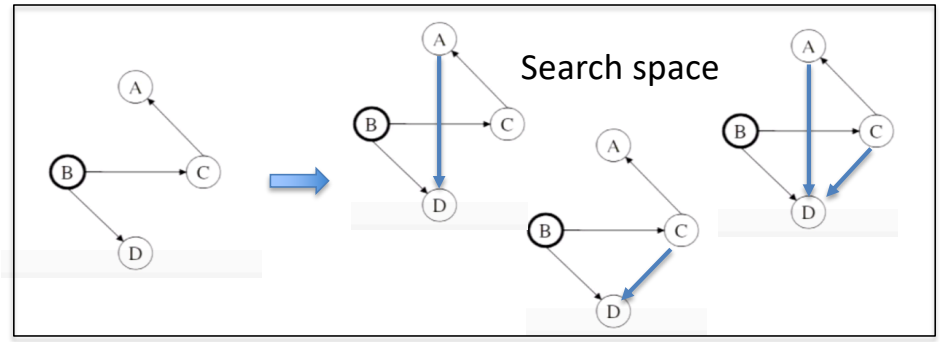
The problem | Step 1 | Step 2

$$\underbrace{P(\mathcal{M} \mid \mathcal{D}) = P(\mathcal{G}, \Theta \mid \mathcal{D})}_{\text{learning}} = \underbrace{P(\mathcal{G} \mid \mathcal{D})}_{\text{structure learning}} \cdot \underbrace{P(\Theta \mid \mathcal{G}, \mathcal{D})}_{\text{parameter learning}}$$

Probability of a model (M) given the data set (D).

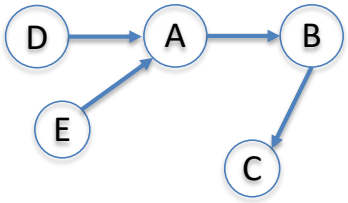
$$\text{Score}(G|\mathcal{D}) \stackrel{def}{=} \text{LL}(G|\mathcal{D}) - \psi(N) \cdot ||G||$$

BIC score = Bayesian Information Criterion



Curse of the dimensionality

- Complexity increases exponentially with respect to:
  - Number of bins each node can take.
  - Number of parent nodes that a node can have.
- Solutions
  - Breaking a huge network into conditionally independent units



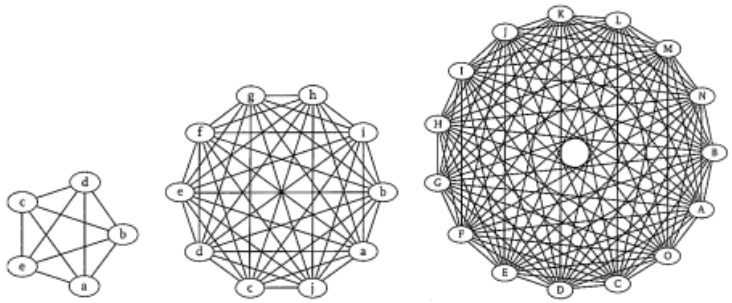
Global distribution

$$P(A,B,C,D,E) = P(D)P(E)P(A|D,E)P(B|A)P(C|B)$$

If each sample has 5 bins

Values to fully enumerate the distribution table: 5^5=1875

Enumerate the Bayesian network: 5 +5 +125 +25 +25=185



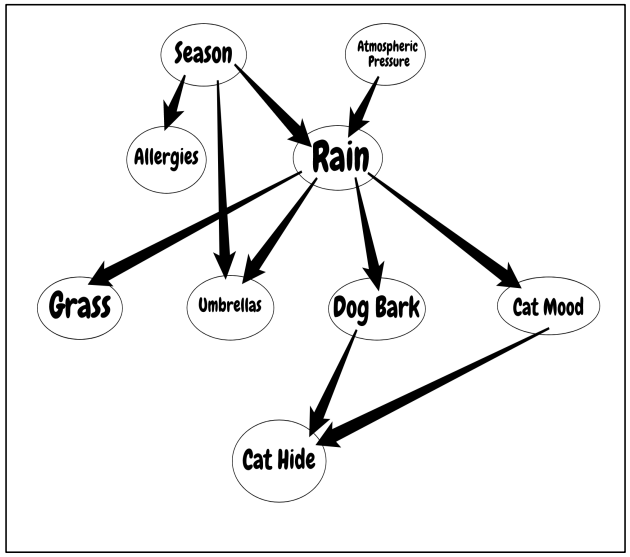
Discussion on Bayesian Network

Pros

- Easy interpretation

Cons

- Requires large computation
- Decomposition of Bayesian seems not efficient



$$P(A \mid B) = \frac{P(B \mid A)P(A)}{P(B)}$$

Demonstration on bnlearn in R

- bnlearn in R
  - Demonstrate the import of data
  - Data structure
  - Output structure
  - Demonstrate how the graph are calculated
  - Import in to Cytoscape for visualization

Thanks!

- Questions?
  - GitHub: https://github.com/niaid/Gene_Regulatory_Networks
  - My email: zhuy16@nih.gov
  - BCBB email: bioinformatics@niaid.nih.gov

Key references

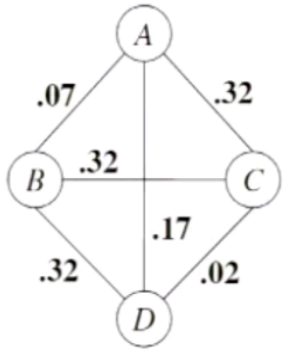
- Intuition understanding about entropy,
  - https://www.youtube.com/watch?v=2s3aJfRr9gE
- Calculation of mutual information using a concrete data sample.
  - https://www.youtube.com/watch?v=3iplfAfGzzI
- CS262a: Learning and reasoning with Bayesian Networks Adnan Darwiche
  - 11a. Learning Parameters: Complete Data (Chapter 17)
    - https://www.youtube.com/watch?v=gRVg0lZgLUg
  - 11b. Learning Parameters: Incomplete Data (Chapter 17)
    - https://www.youtube.com/watch?v=NDoHheP2ww4
  - 12a. Learning Network Structure I (Chapter 17)
    - https://www.youtube.com/watch?v=RV2lInyq_bI
  - 12b. Learning Network Structure II (Chapter 17)
    - https://www.youtube.com/watch?v=o-urnZRNnbY
- Bnlearn https://www.youtube.com/watch?v=4JkddqxGrO0

Other resources

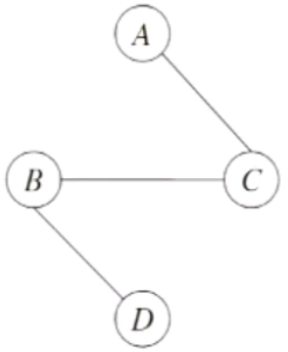
- GraphPlot, http://juliagraphs.github.io/GraphPlot.jl/
- Gamma distribution, https://towardsdatascience.com/gamma-distribution-intuition-derivation-and-examples-55f407423840
- R packages
  - `install.packages("igraph")`
  - `install.packages("bnlearn")`
  - `BiocManager::install("Rgraphviz")`
- iGraph for network analysis https://www.bioss.ac.uk/people/helen/igraphIntro.html
- https://www.r-bloggers.com/interactive-network-visualization-with-r/

Learning the skeleton of a graph

- Constructing a tree structure (each node can only have one parent node.
- Step 1, learning the Maximum Spanning Tree.
- Add direction through starting from a randomly node.
- The resulting directed graph will be used as seed for other algorithms.
- Optimization of a graph, a commonly used approach constrained on a penalty on the complexity (||G||) of the graph.



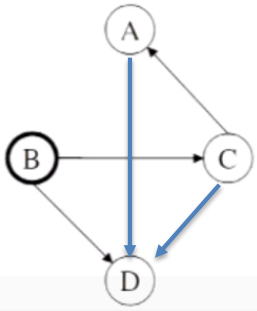
(a) mutual information graph

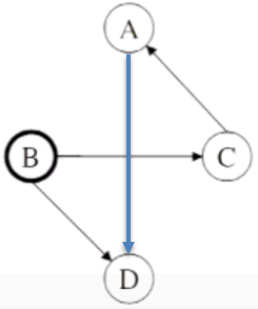


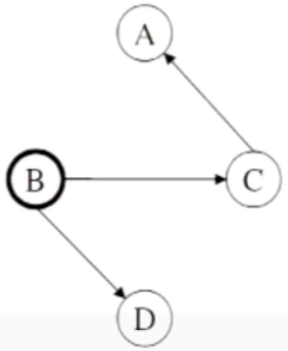
(b) maximum spanning tree

$$\text{Score}(G|\mathcal{D}) \overset{def}{=} \text{LL}(G|\mathcal{D}) - \psi(N) \cdot ||G||$$

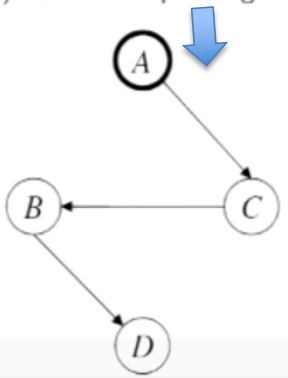
BIC score = Bayesian Information Criterion







(c) maximum likelihood tree

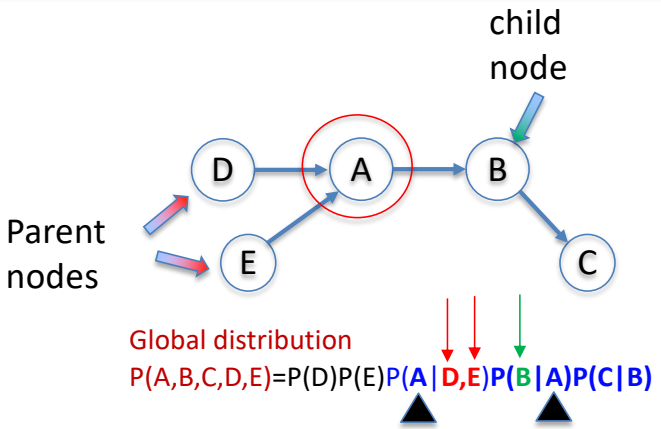


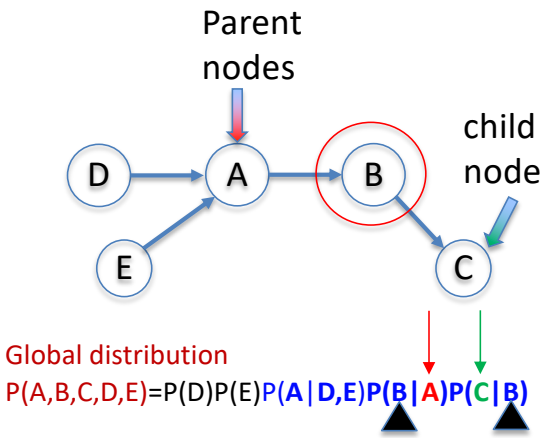
(d) maximum likelihood tree

https://www.youtube.com/watch?v=o-urnZRNnbY

Parent nodes and child node

- To a given node
  - Conditional nodes (reasons or contributing factors) are called parents.
  - The consequent nodes are child nodes.





Objective function for optimizing structures

The problem — Step 1 — Step 2

$$\underbrace{\mathrm{P}(\mathcal{M} \mid \mathcal{D}) = \mathrm{P}(\mathcal{G}, \Theta \mid \mathcal{D})}_{\text{learning}} = \underbrace{\mathrm{P}(\mathcal{G} \mid \mathcal{D})}_{\text{structure learning}} \cdot \underbrace{\mathrm{P}(\Theta \mid \mathcal{G}, \mathcal{D})}_{\text{parameter learning}}$$

Probability of a model (M) given the data set (D).

$$\mathrm{MI}_{\mathfrak{D}}(X, U) \stackrel{def}{=} \sum_{x,u} \mathrm{Pr}_{\mathfrak{D}}(x, u) \log \frac{\mathrm{Pr}_{\mathfrak{D}}(x, u)}{\mathrm{Pr}_{\mathfrak{D}}(x)\mathrm{Pr}_{\mathfrak{D}}(u)}$$

$$\mathrm{Score}(G|\mathfrak{D}) \stackrel{def}{=} \mathrm{LL}(G|\mathfrak{D}) - \psi(N) \cdot ||G||$$

Degree of a network
Sum of the number of possible states each node can possibly take

$$||G|| \stackrel{def}{=} \sum_{i=1}^{n} ||X_i \mathbf{U}_i||$$

$$||X_i \mathbf{U}_i|| \stackrel{def}{=} (X_i{}^{\#} - 1)\mathbf{U}_i{}^{\#}$$

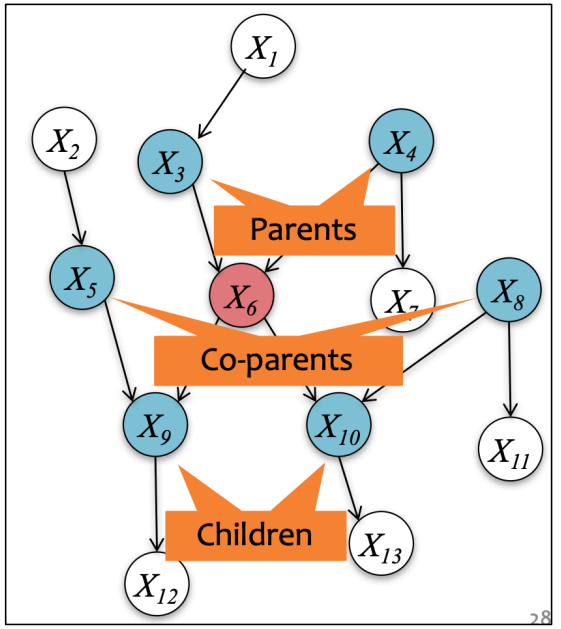
N: the number of nodes in the network

How to set up a tunnel to server

- install.packages('IRkernel') # Don’t forget step 2/2!
- IRkernel::installspec()
- using Pkg
- Pkg.add("IJulia")
- user@local_machine$ ssh -N -L localhost:8888:localhost:8888 user@remote_mahcine
- Paste this to the url to access the Julia –"localhost:1234"

Computation: how to break up a huge network to small local problems

- Optimization of the local variables
  - For computation purpose, you need to break a huge network into smaller pieces.
  - for a node in a graphical model, **Markov blanket** contains all the variables needed to do approximation, that shield the node from the rest of the network.



Ref: Learning Bayesian network structure using Markov blanket decomposition, Bui 2012

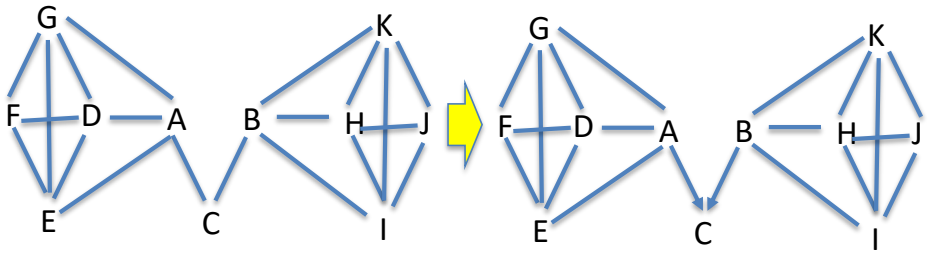
Assign directions: Induction of Causality algorithm

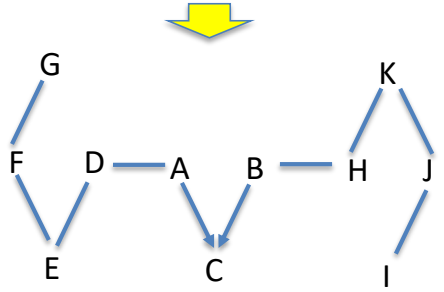
The Induction of Causality Algorithm:
If,

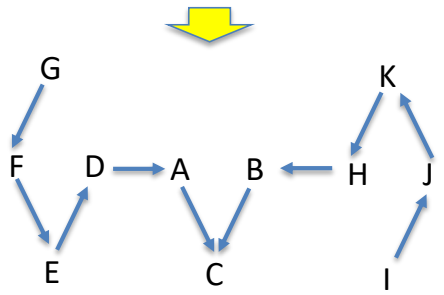
1. A, B are not connected through any other connection.
2. A and B have a common connection to C

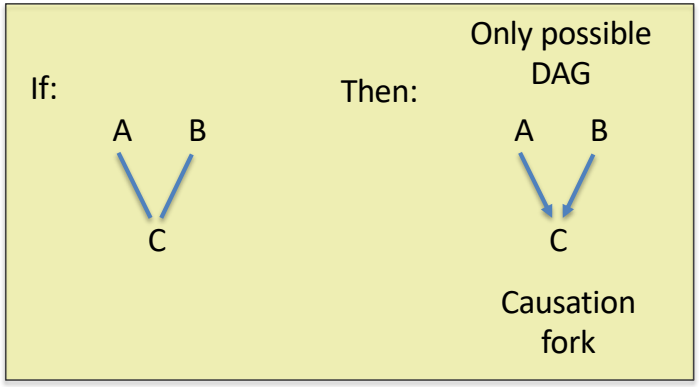
Then:

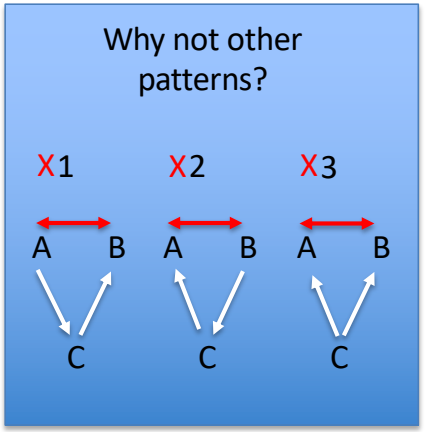
arrows point from A and B to C



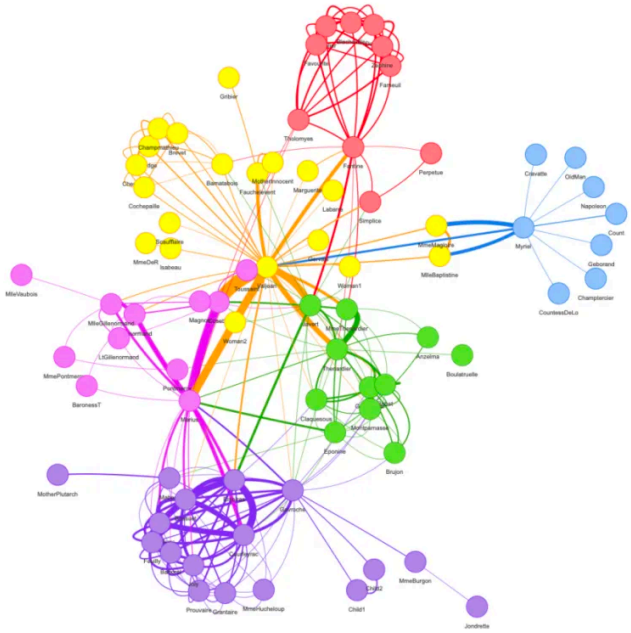








- > tpm=read.table("S_GSE71485_Single_TPM.txt",row.names=1,header=T)
- > Tpm=tpm[rowMeans(tpm)>100,]
- > write.table(Tpm,"S_GSE71485_Single_TPM.txt")



Parameters in Bayesian network

likelihood prior

$$P(A \mid B) = \frac{P(B \mid A)P(A)}{P(B)}$$

posterior Evidence

posterior likelihood prior

$$\mathbf{P(cold|winter)} = \frac{P(\boldsymbol{winter}|\boldsymbol{cold})P(cold)}{P(winter)} = \frac{P(\boldsymbol{winter}|\boldsymbol{cold})P(cold)}{P(winter)} = \frac{100\% * 25\%}{25\%} = 100\%$$

Evidence

Infer the parameters in Bayesian network

Expectation Maximization

- Assign a set of random parameters θ^0.
- Based on evidence samples, calculate the distribution of each sample.
- Go through all the samples.
- Construct the averaged distribution.
- Based on the averaged distribution, recalculate the set of parameters θ^1.
- Repeat the previous step until θ^{K+1} and θ^K converges.

Using log-likelihood as a objective function to maximize

- Construct Log Likelihood formula.
- Use classical methods such as gradient decent to optimize the parameter with a assigned learning rate, to iterate and reach a local maximum.

For complete data

$$\theta^\star = \underset{\theta}{\operatorname{argmax}}\, \mathrm{L}(\theta|\mathcal{D})$$

$$\text{iff } \theta^\star_{x|\mathbf{u}} = \Pr_{\mathcal{D}}(x|\mathbf{u})$$

For incomplete data