Complexity in Medicine From Intracellular Network to Brain Network

Prof. Anastasios Bezerianos

BIOSIGNAL LABORATORY
DEPT OF MEDICAL PHYSICS
SCHOOL OF MEDICINE
UNIVERSITY OF PATRAS

COGNITIVE ENGINEERING LAB
SINGAPORE
INSTITUTE FOR NEUROTECHNOLOGY
NATIONAL UNIVERSITY OF SINGAPORE

Summer School
"Complexity and Dynamic Systems"
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Introduction

I. Basic Concepts
II. Introduction to Biology
III. Introduction to Biological Networks
IV. Gene Regulatory Networks
V. Protein-Protein Interactions Network
VI. Cell Signaling Networks (Pathway)

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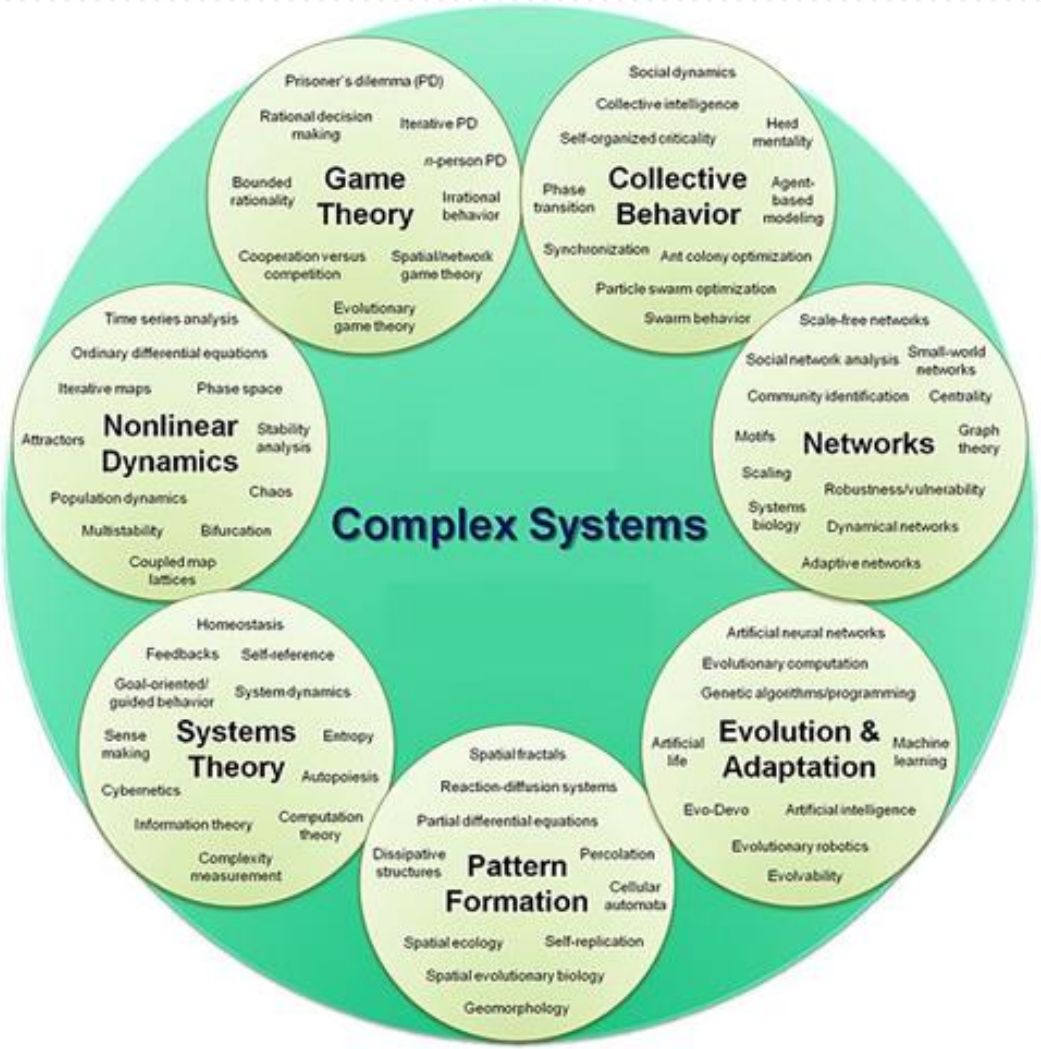
Complex Systems

- Studying how relationships between parts give rise to the collective behaviors of a system and how the system interacts and forms relationships with its environment.



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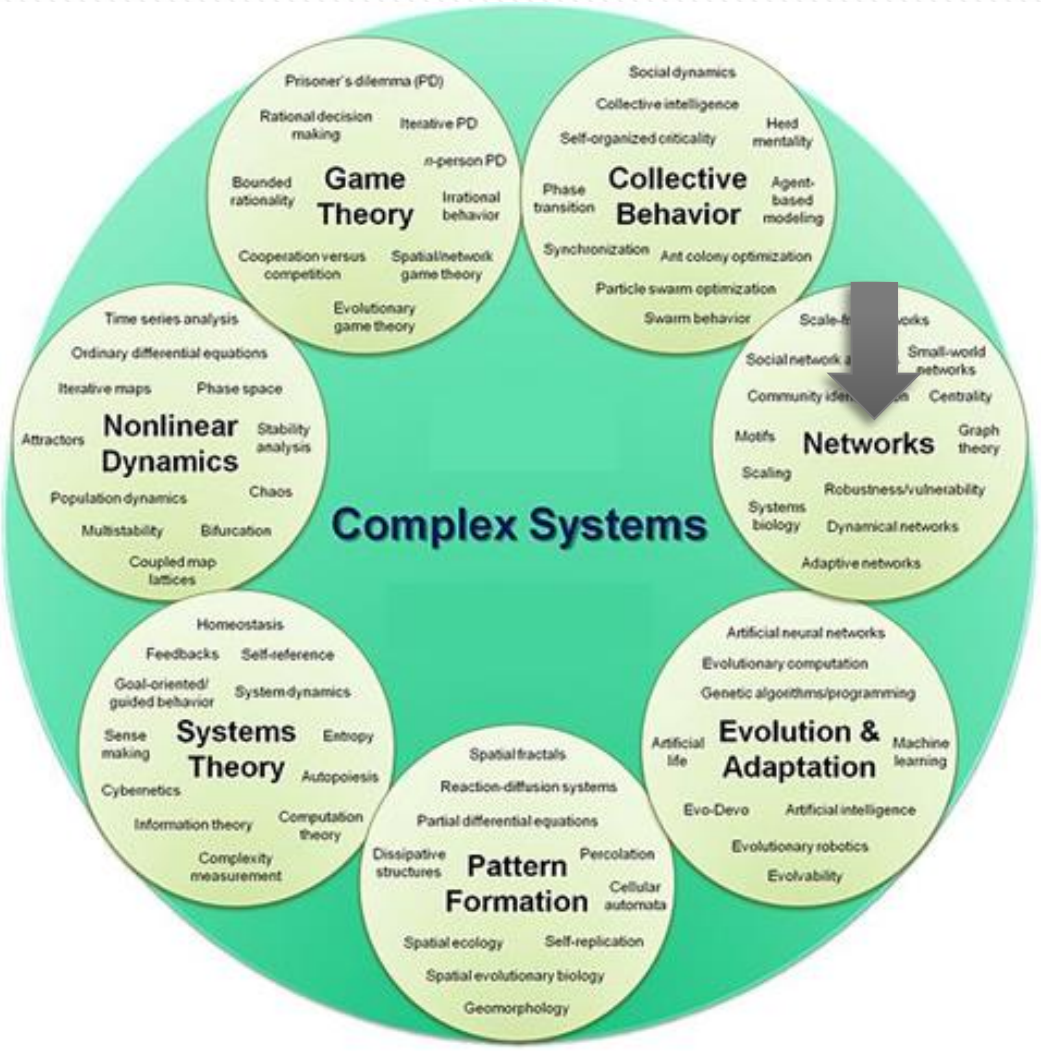
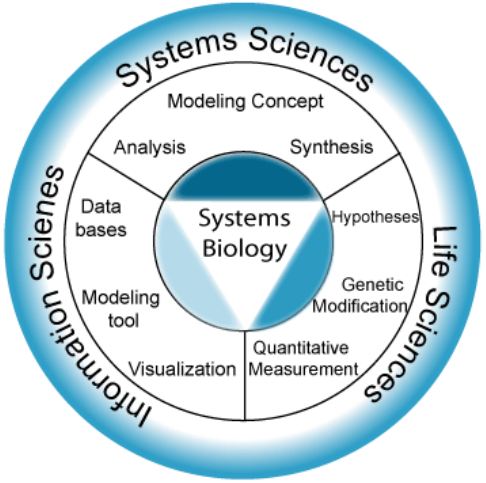
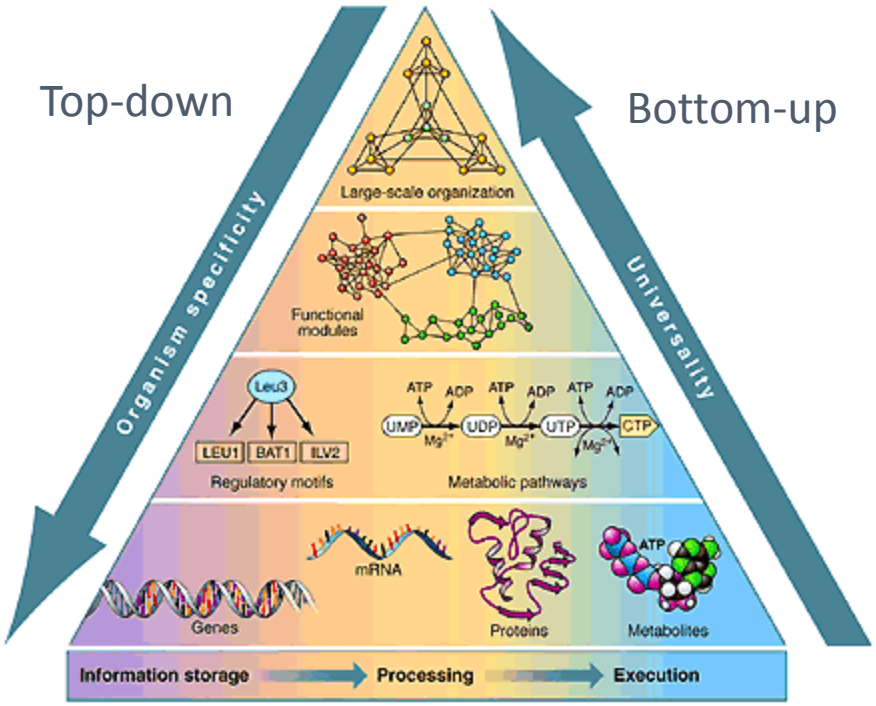


Systems Biology

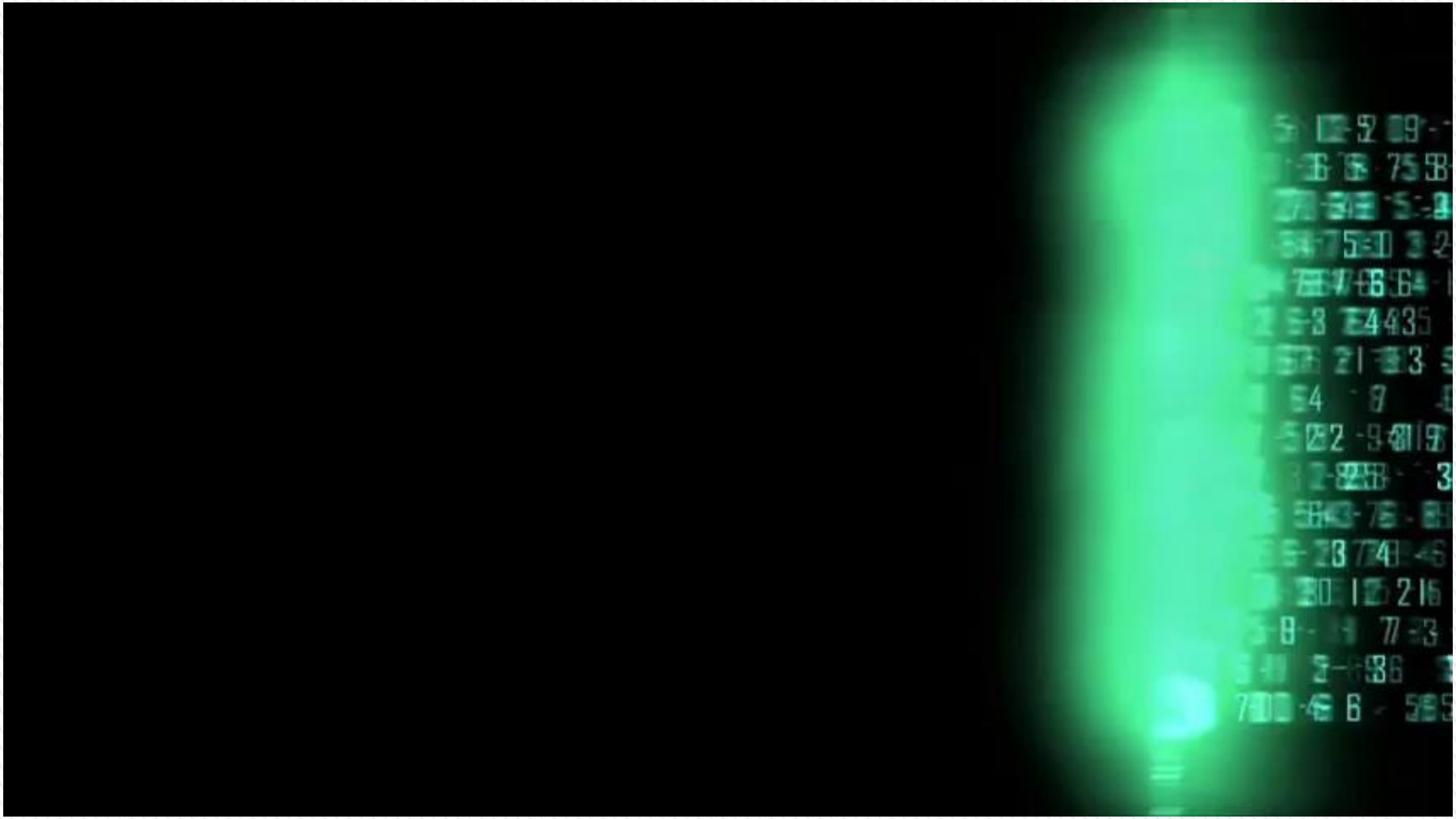
- Systems biology is the study of an organism, viewed as an integrated and interacting network of genes, proteins and biochemical reactions which give rise to life.
- The focus is on a complete system made up of different parts interacting with each other.
- Based on the philosophy that the whole is greater than the sum of the parts.
- From the particular to the universal.
  - Level 1: Central dogma of molecular biology
  - Level 2: Regulatory Interactions
  - Level 3: Functional modules (subnetworks) from level 2
  - Level 4: A scale-free hierarchical architecture from functional modules





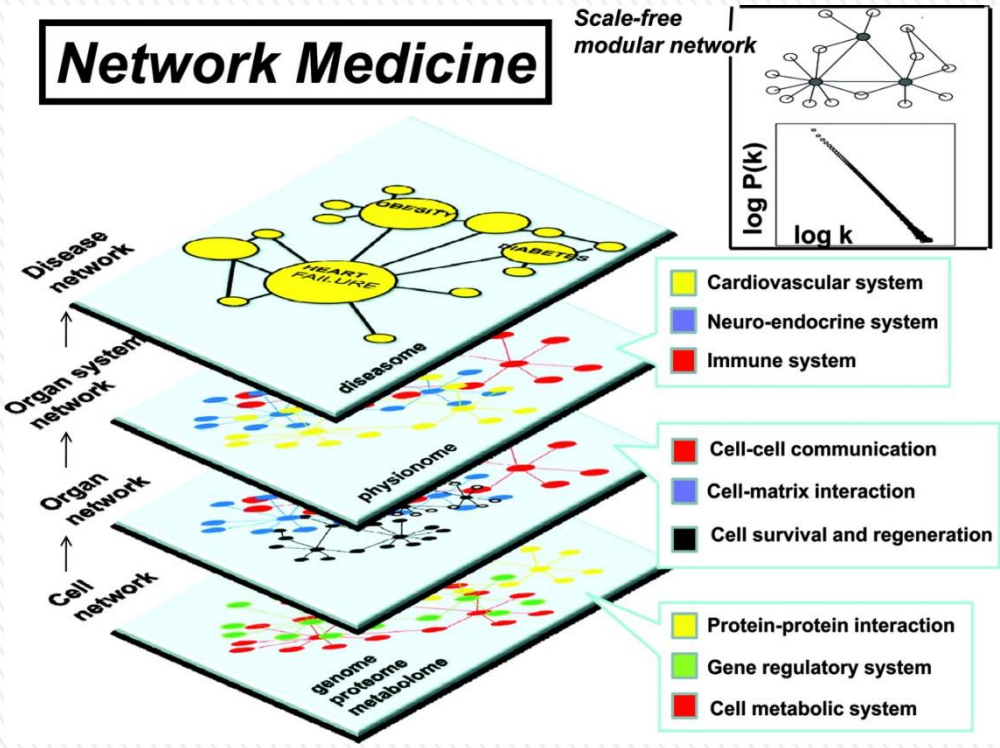
Life's Complexity Pyramid

Systems Biology



Systems Medicine

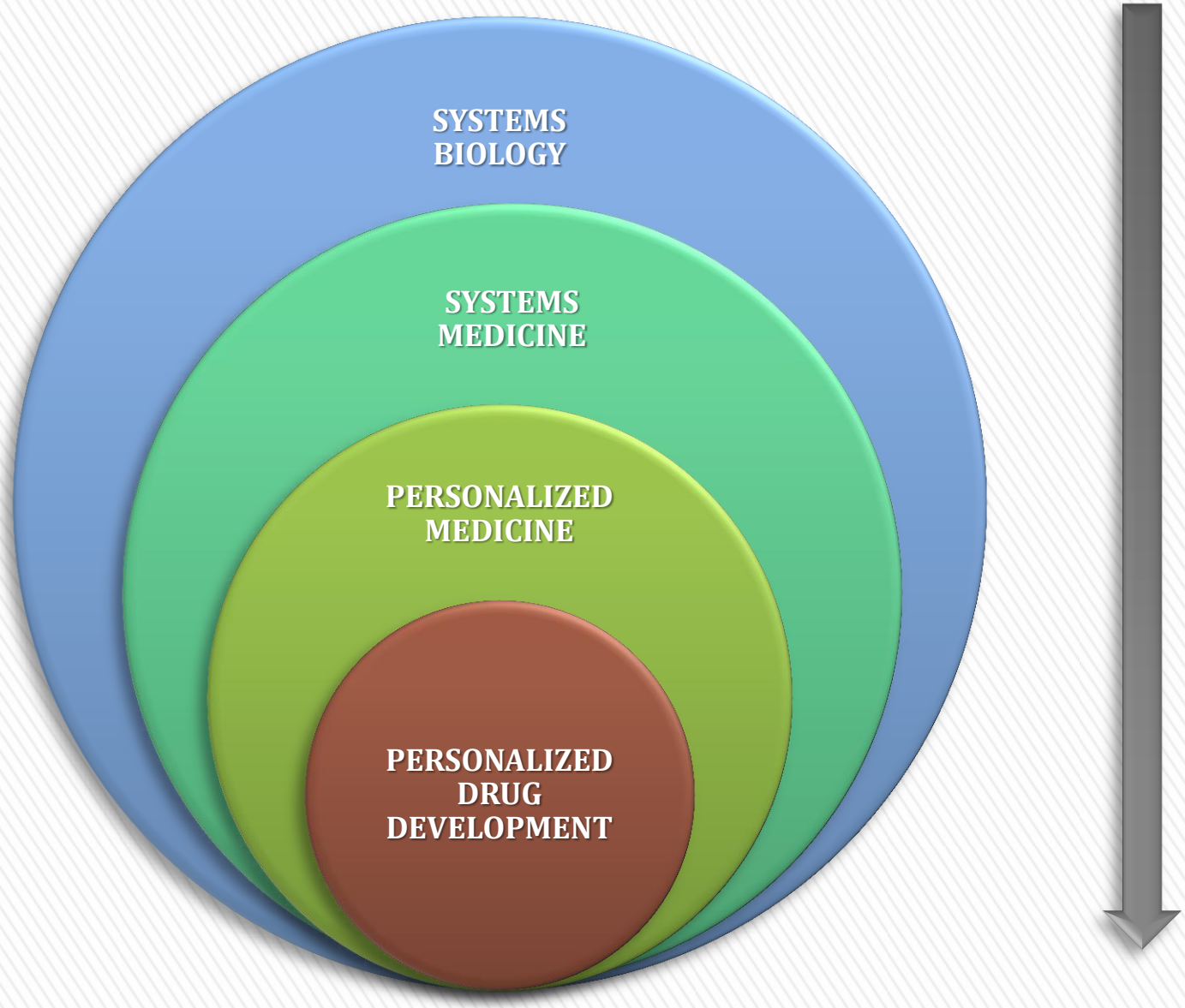
- ***Systems medicine*** is an inter-disciplinary field of study that looks at the dynamic systems of the human body as part of an integrated whole, incorporating biochemical, physiological, and environment interactions that sustain life.
- Systems medicine draws on theories from holistic medicine, systems science and systems biology



Systems biology approach to medicine creates network medicine

Systems Medicine

From Systems Biology to Personalized Drug Development



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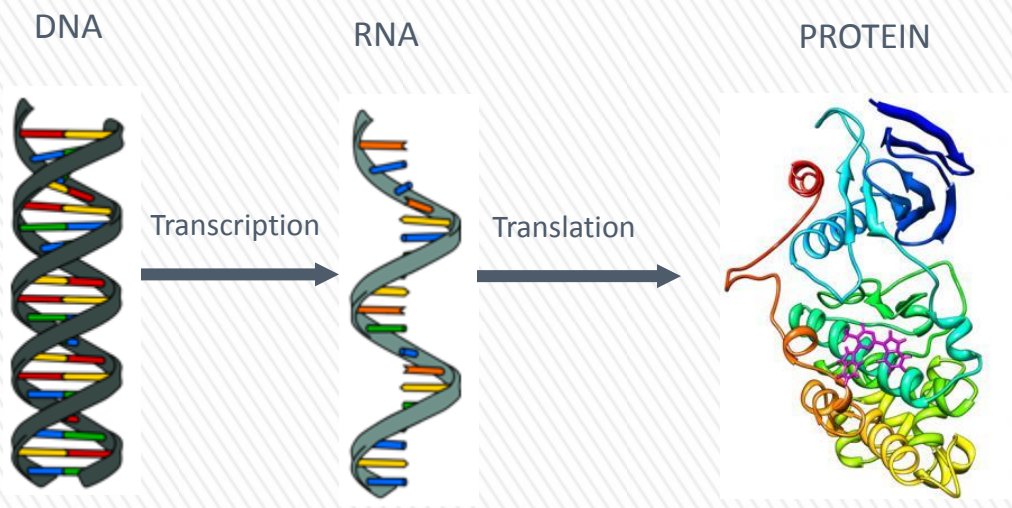
Introduction to Biology - Background Knowledge

- Cell reproduction, metabolism, and responses to the environment are all controlled by proteins
- Some genes regulate other genes (via the proteins they produce)
- Central Dogma of Molecular Biology:

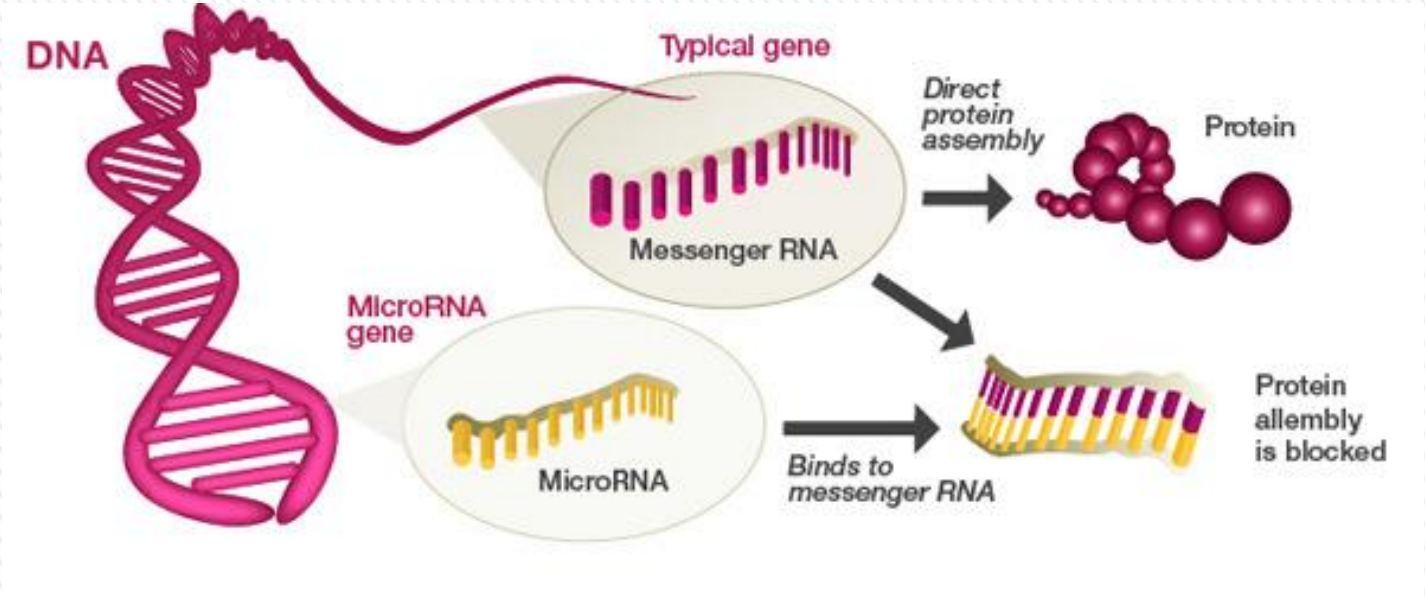
  Model regulation of *gene expression*

  - Recall: gene → mRNA → protein



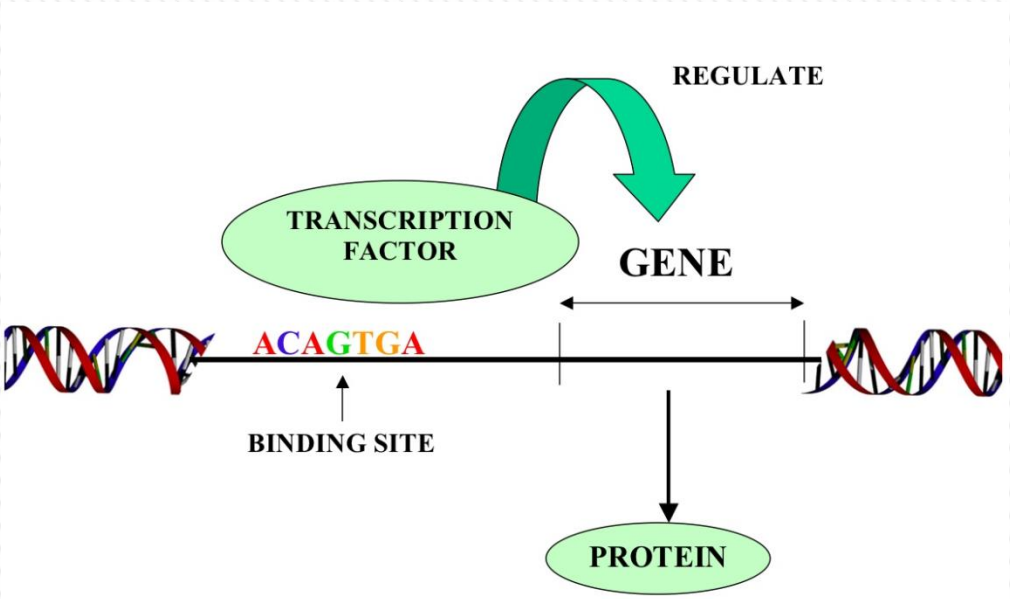
MicroRNA

- Non-coding RNA double stranded
- 19-22nt long
- Represses (or activates in few cases) the activity of complementary mRNA
- Controls the 30% of the gene products in mammals
- 1 miRNA targets hundreds of mRNAs



Transcription Factor

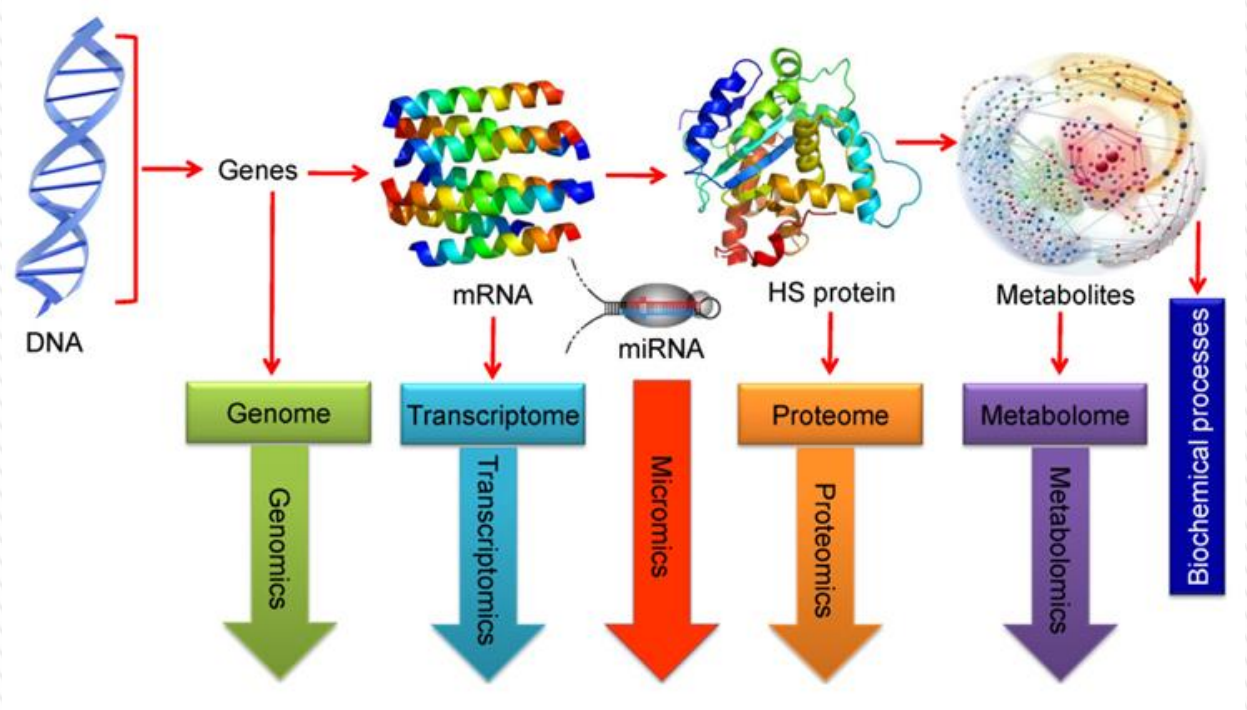
- Is a protein that binds to specific DNA sequences, thereby controlling the flow (or transcription) of genetic information from DNA to messenger RNA
- Transcription factors perform this function alone or with other proteins in a complex, by promoting (as an activator), or blocking (as a repressor) the recruitment of RNA polymerase (the enzyme that performs the transcription of genetic information from DNA to RNA) to specific genes.



Omics Data

- Refers to a field of study in biology ending in -omics, such as
  - genomics, proteomics, Metabolomics, Transcriptomics, Micromics

- Omics aims at the collective characterization and quantification of pools of biological molecules that translate into the structure, function, and dynamics of an organism or organisms.

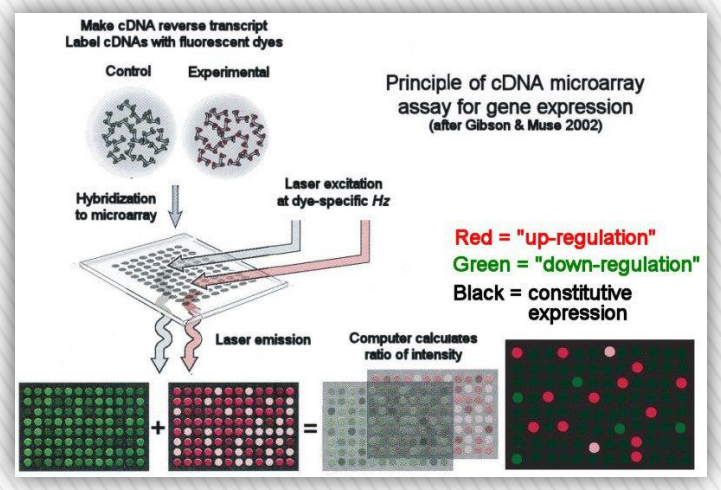


Omics Data

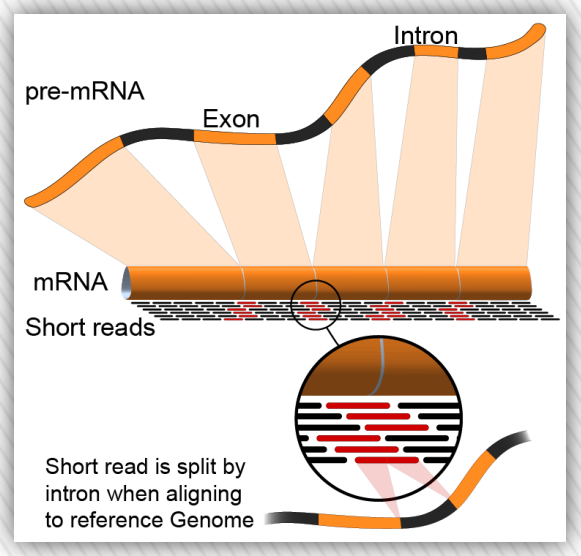
- ***Genomics***
  - Sub discipline of genetics devoted to the mapping, sequencing and functional analysis of genomics
- ***Transcriptomics***
  - Complete set of RNA transcripts that are produced by the genome, under specific circumstances or in a specific cell
- ***Proteomics***
  - Study of the proteome, which is the protein complement of the genome
- ***Metabolomics***
  - Study of chemical processes involving metabolites

Omics Techniques

- ***Microarrays:***
  - Measure mRNA abundance for each gene
  - The amount of transcribed mRNA correlates with g*ene expression:*
  - Gene expressions indicates the rate at which a gene produces the corresponding protein

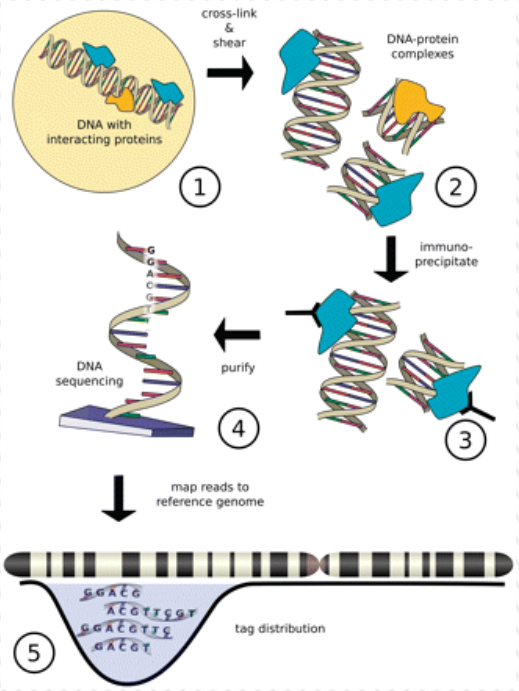


- ***RNA-Seq (RNA Sequencing)***
  - is a technology that uses the capabilities of next-generation sequencing to reveal a snapshot of RNA presence and quantity from a genome at a given moment in time
  - also called "Whole Transcriptome Shotgun Sequencing



Omics Techniques

- ***Chip-Seq:***
  - Is a method used to analyze protein interactions with DNA.
  - ChIP-seq combines chromatin immunoprecipitation (ChIP) with massively parallel DNA sequencing to identify the binding sites of DNA-associated proteins
  - Output:
    - TF - Genes and TF - microRNAs relations



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History

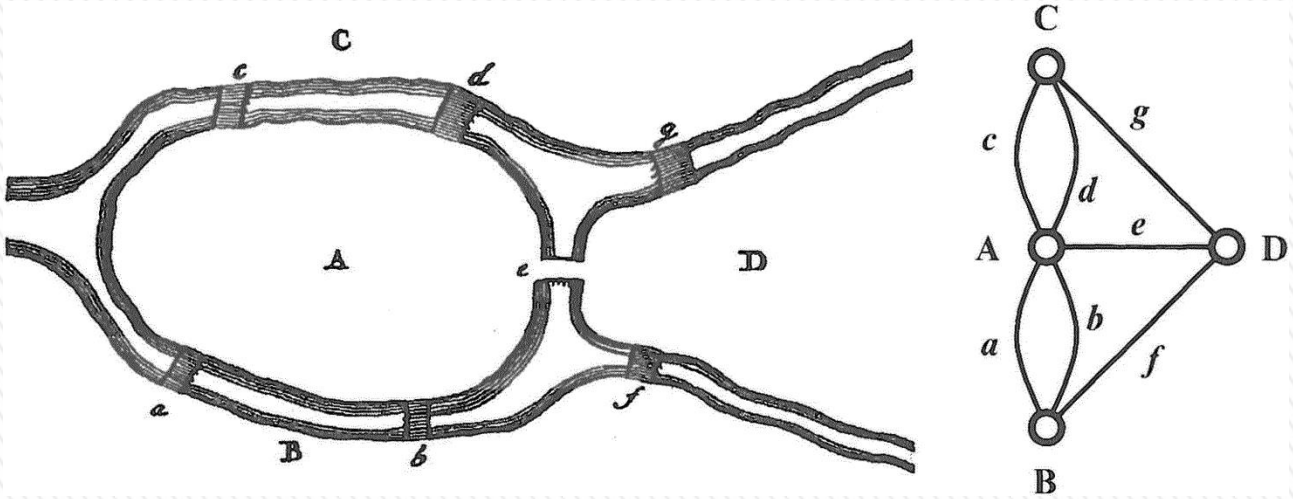
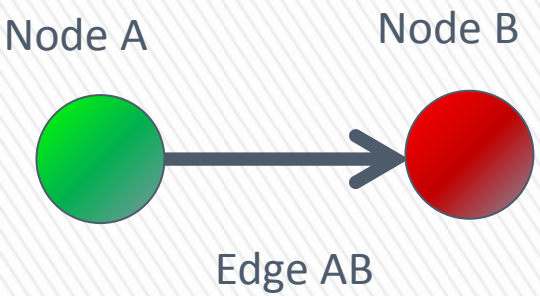


Fig.1 Euler's solution to the Konigsberg bridge problem (1736). The illustration on the left is from Euler's original paper and shows the river Pregel and its seven bridges joining four landmasses. The illustration on the right is the graphical representation of the problem – landmasses have been replaced by nodes and bridges by edges.

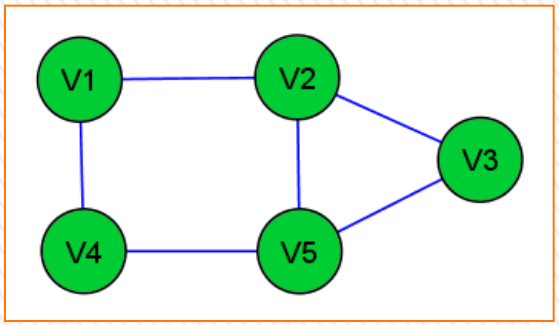
Euler showed that a path that traverses all bridges exactly once and leads back to the point of origin is impossible.

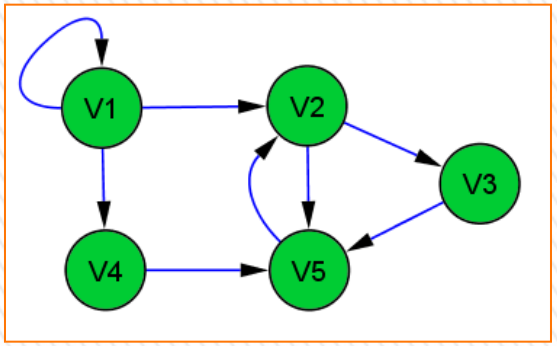
Introduction to Biological Networks

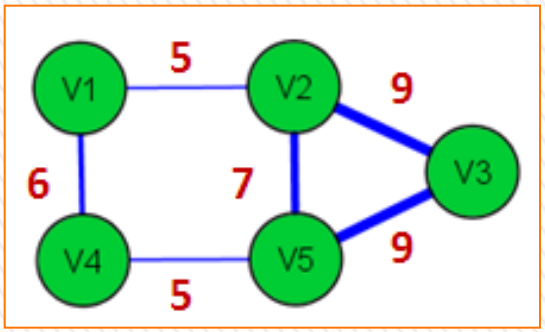
- ***Nodes or vertices***
  - Genes, mRNA, miRNAs, proteins, peptide, non-protein biomolecules etc.
- ***Edges or links between pairs of nodes.***
  - Captures pairwise relationship between objects.
  - Causal relationship, Biological relationships, interactions, regulations, reactions, transformations, activation, inhibitions etc.



From Networks to Matrices







Adjacency matrices

	V1	V2	V3	V4	V5
V1	0	1	0	1	0
V2	1	0	1	0	1
V3	0	1	0	0	1
V4	1	0	0	0	1
V5	0	1	1	1	0

	V1	V2	V3	V4	V5
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V3	0	0	0	0	1
V4	0	0	0	0	1
V5	0	1	0	0	0

	V1	V2	V3	V4	V5
V1	0	5	0	6	0
V2	5	0	9	0	7
V3	0	9	0	0	9
V4	6	0	0	0	5
V5	0	7	9	5	0

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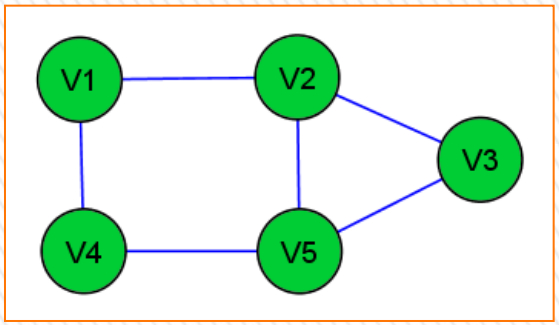

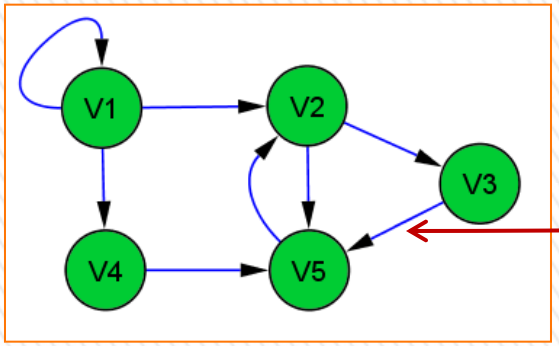

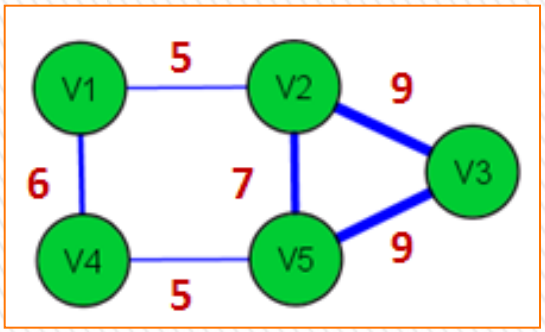

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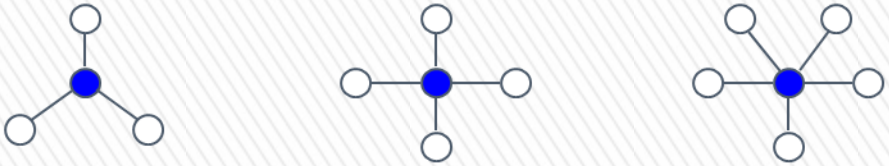
	V1	V2	V3	V4	V5
V1	0	5	0	6	0
V2	5	0	9	0	7
V3	0	9	0	0	9
V4	6	0	0	0	5
V5	0	7	9	5	0

Main Network features

Paths

Stars



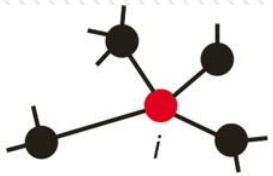
Cycles

Complete Graphs

Bipartite Graphs

Topological Metrics

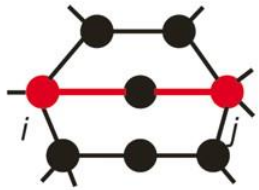
A



Degree

k_i = number of links connected to node *i*

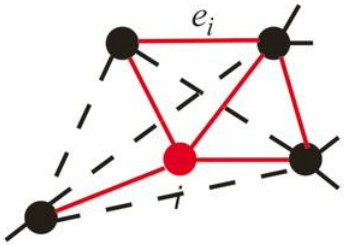
B



Distance

d_{ij} = shortest path length between node *i* and *j*

D

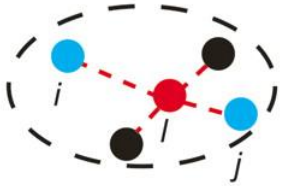


Clustering Coefficient

$$c_i = \frac{2e_i}{k_i(k_i - 1)}$$

e_i : number of existing links (labeled in red) among the k_i nodes that connect to node *i*

E



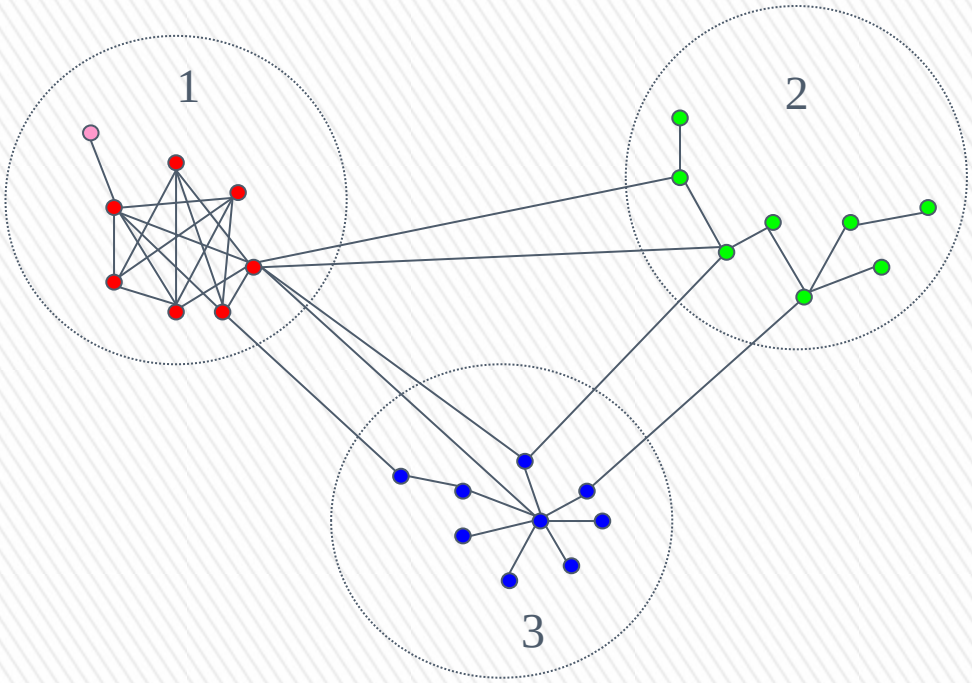
Betweenness $b_l = \sum_{ij} p_{ij}(l) / p_{ij}$

p_{ij} : number of shortest paths between *i* and *j*

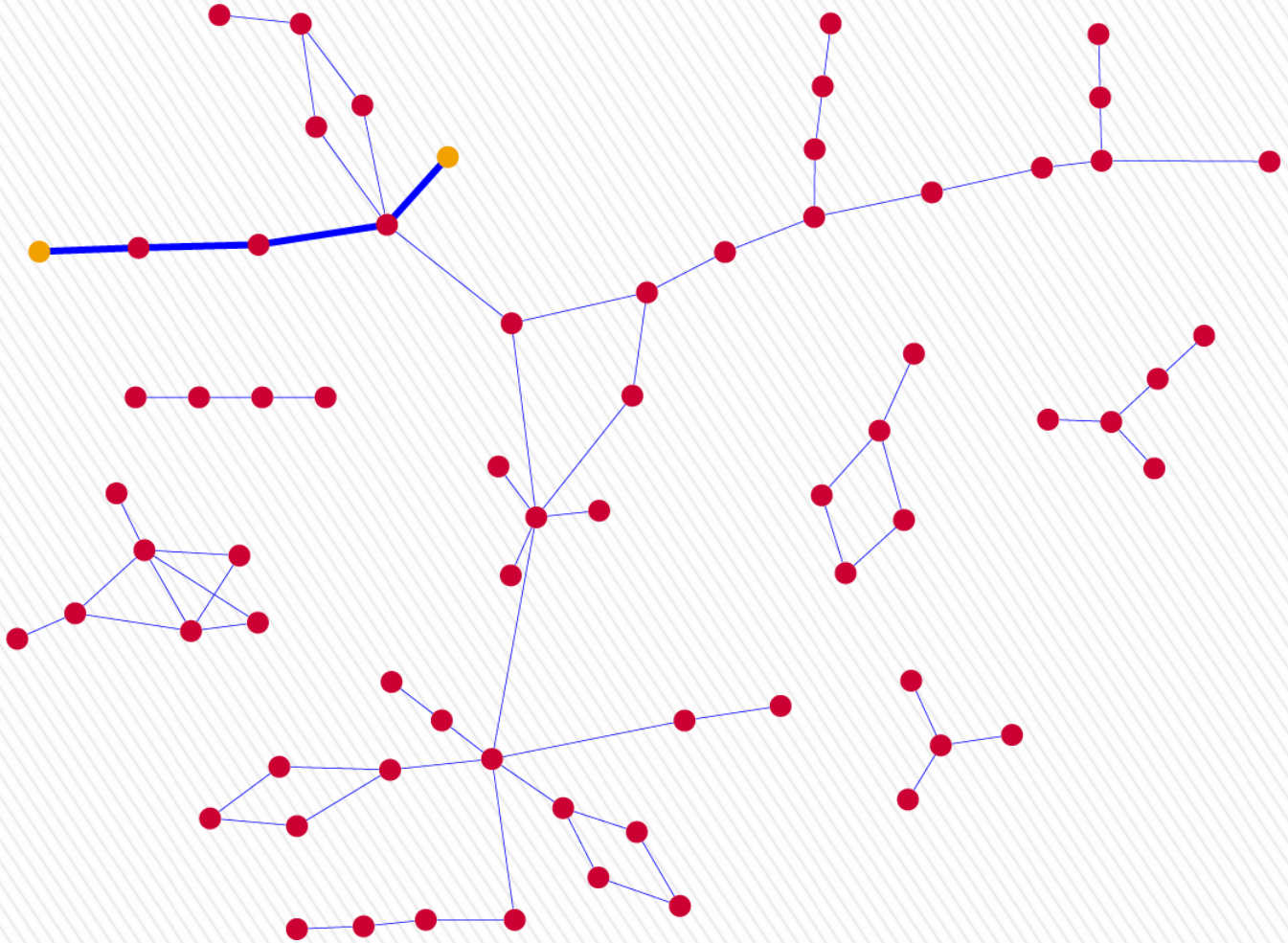
$p_{ij}(l)$: number of shortest paths between *i* and *j* going through node *l*

Functional Modules in Biological Networks

- A “module” in a biological system is dense sub-network with distinct functional role
- Functional modules will be reflect in the topological structures of biological networks.
- Identifying functional modules and their relationship from biological networks will help to the understanding of the organization, evolution and interaction of the cellular systems they represent



Shortest Path between Nodes



Shortest path: Connect two nodes by as few edges as possible

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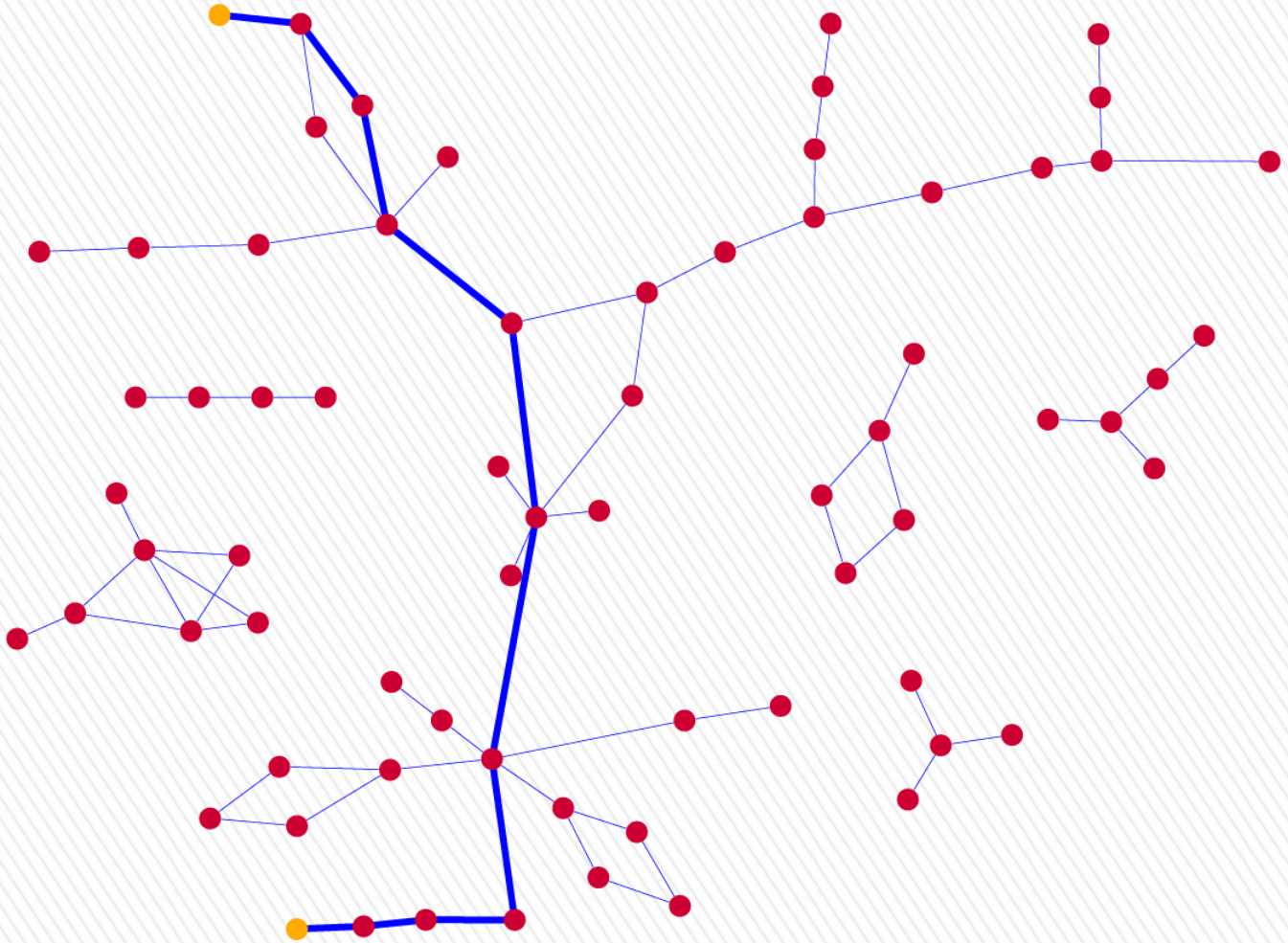
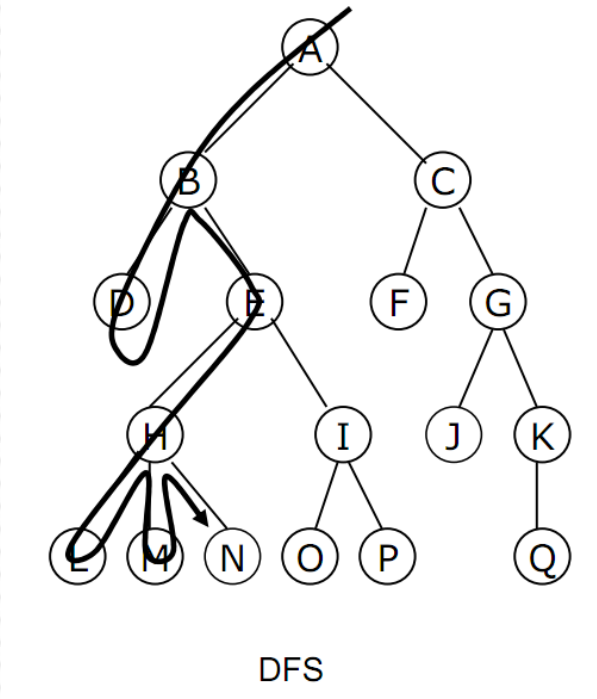


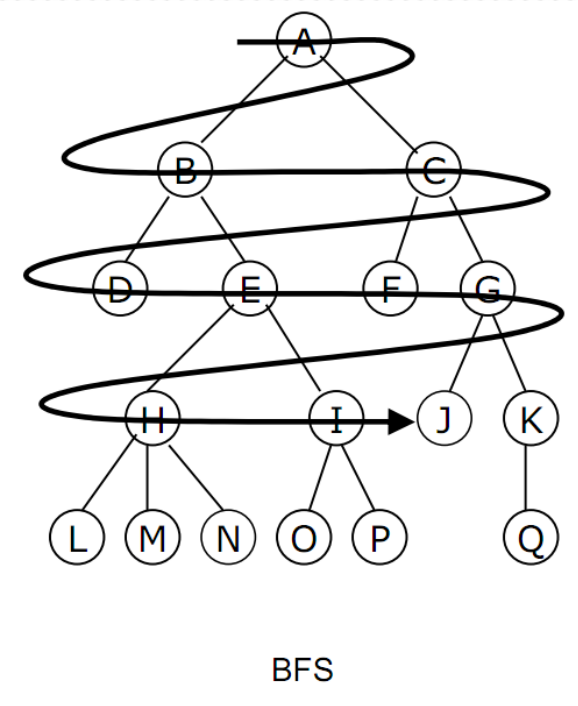
Shortest path: Connect two nodes by as few edges as possible

Graph Traversing

- Given a graph G(V,E), explore every vertex and every edge
- Using adjacency list is more efficient
- Example algorithms:
  - Depth-first search (DFS)
  - Breadth-first search (BFS)



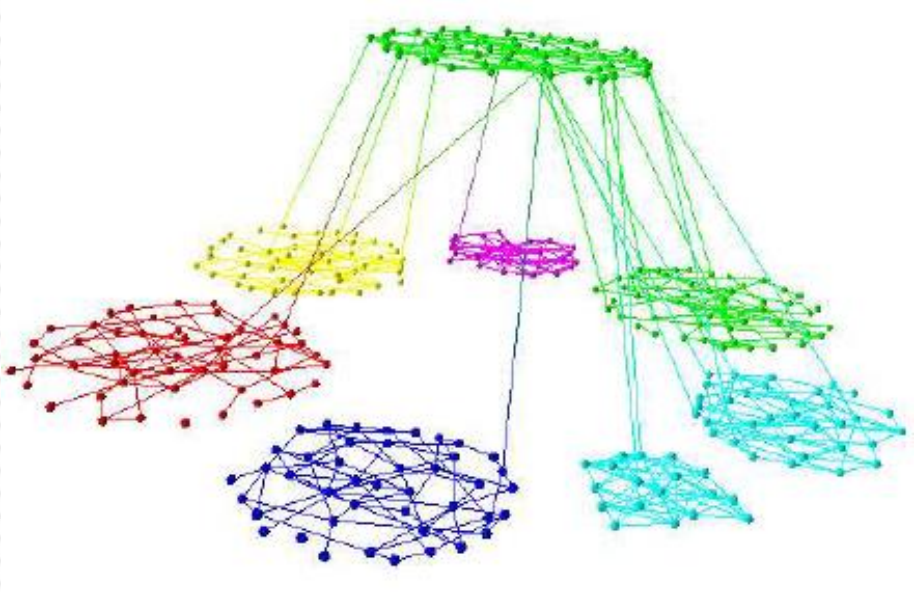
DFS



BFS

Graph Clustering

- The task of grouping the vertices of the graph into groups (clusters) taking into consideration
  - the edge structure of the graph in such a way that
  - there should be many edges within each cluster and relatively few between the clusters



Types of Biological Networks

- Intra-cellular networks
- Neuronal synaptic connection networks
- Brain functional networks
- Ecological food webs
- Phylogenetic networks
- Correlation networks (e.g., gene expression)
- Disease – “disease gene” association networks
- Drug – “drug target” networks

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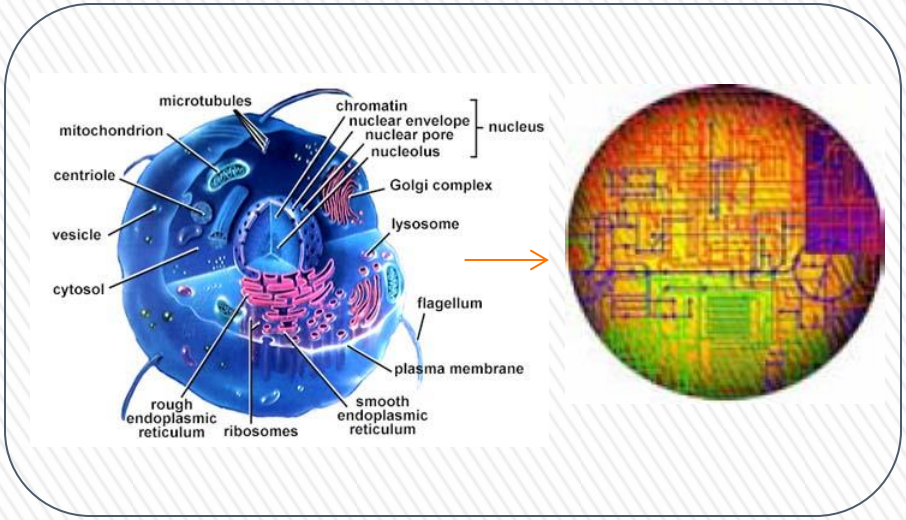
Intra-cellular networks

- Types of Intra-cellular networks
  - Metabolic networks
  - Gene regulatory networks
  - Cell signaling networks (Pathways)
  - Protein-protein interaction (PPI) networks
  - Protein structure networks



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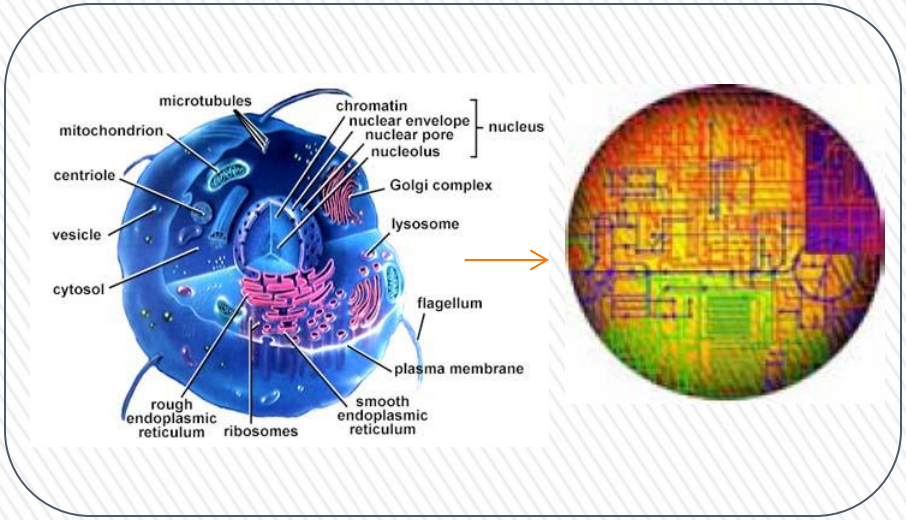

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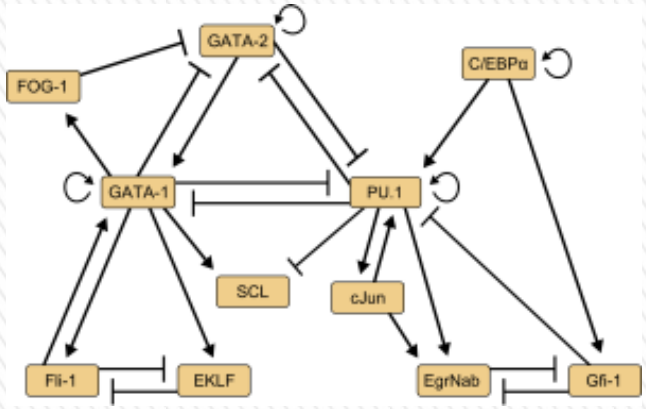
Gene regulatory networks

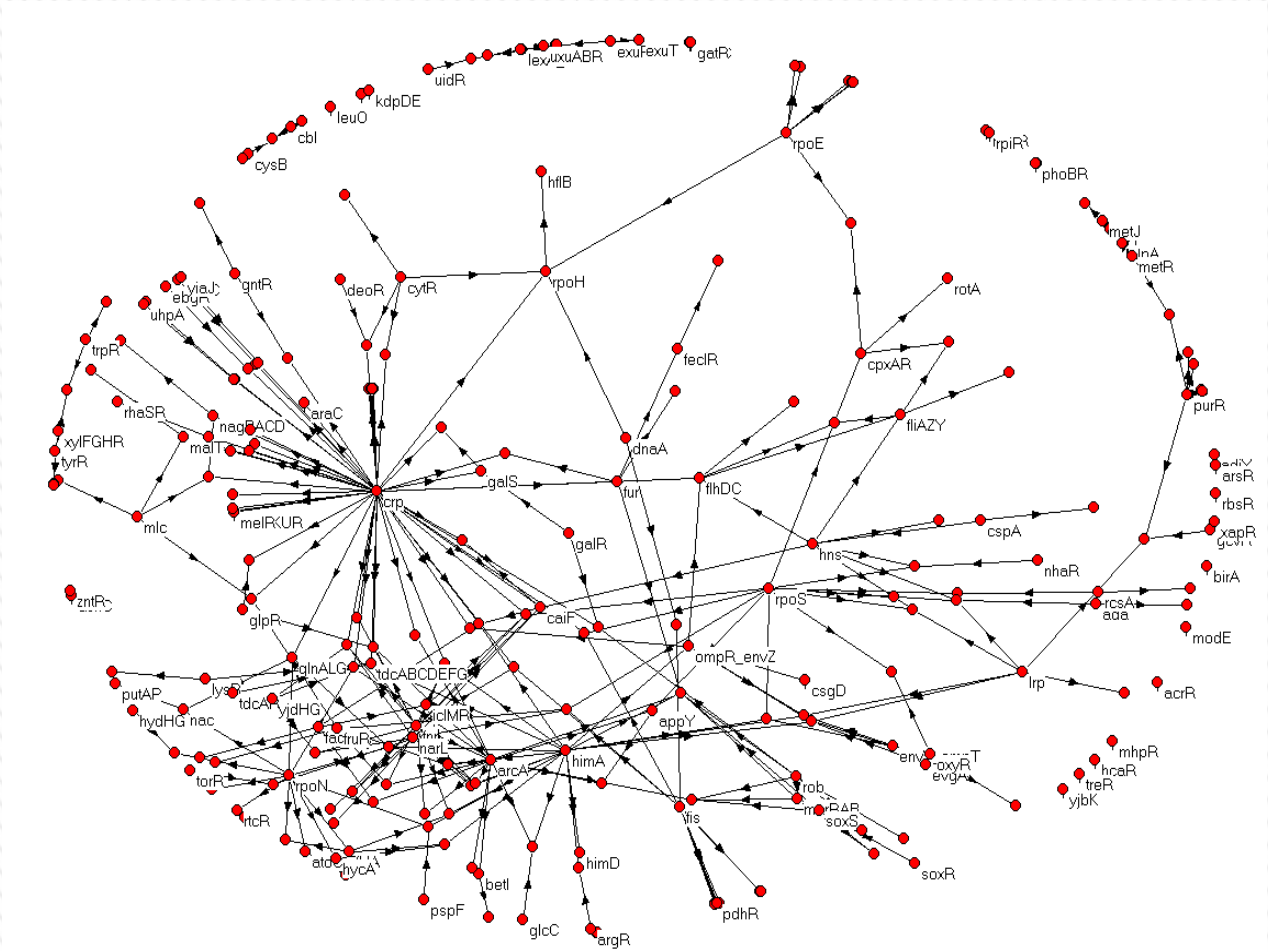
- The construction of GRNs is based on gene expressions data (microarrays, RNA-Seq)
- Nodes correspond to genes
- Directed edges correspond to interactions through which the products of one gene affect those of another

- Transcription factor X (protein product of gene X) binds regulatory DNA regions of gene Y to regulate the production rate (i.e., stimulate or repress transcription) of protein Y
- Note: proteins are products of gene expression that play a key role in regulation of gene expression



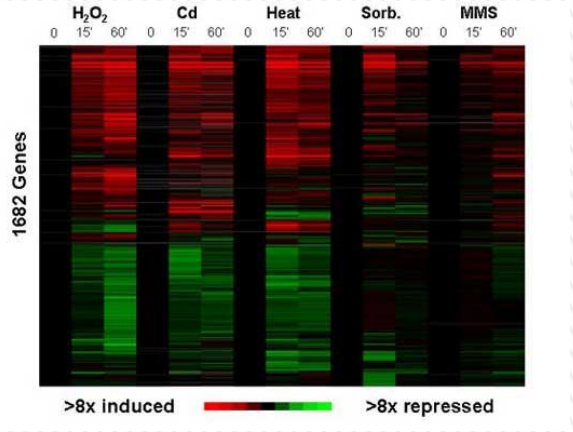
Gene regulatory networks: An example

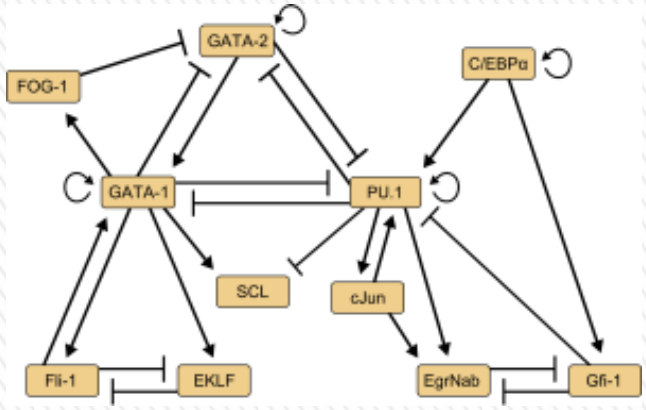
- The gene regulatory network of E. coli
  - Nodes = proteins (or the genes that encode them)
  - Edges = regulatory relation between two proteins



Gene regulatory networks Reconstruction

- Goal: Construct gene networks based on gene expression data

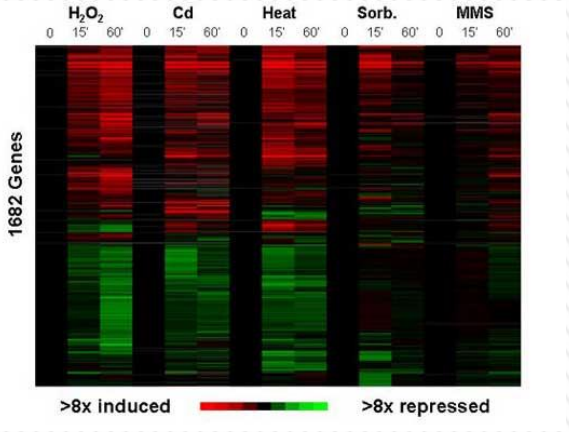


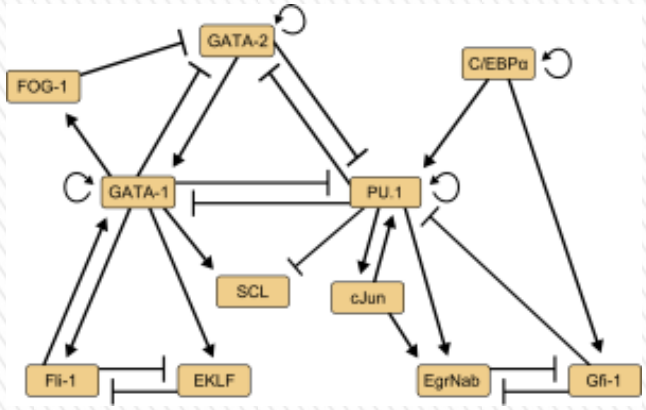


- GRN Reconstruction modeling techniques
  - Linear Model
  - Bayesian Networks
  - Differential Equations
  - Boolean Network
  - Neural Networks
  - Hybrid models

Gene regulatory networks Reconstruction

- Goal: Construct gene networks based on gene expression data

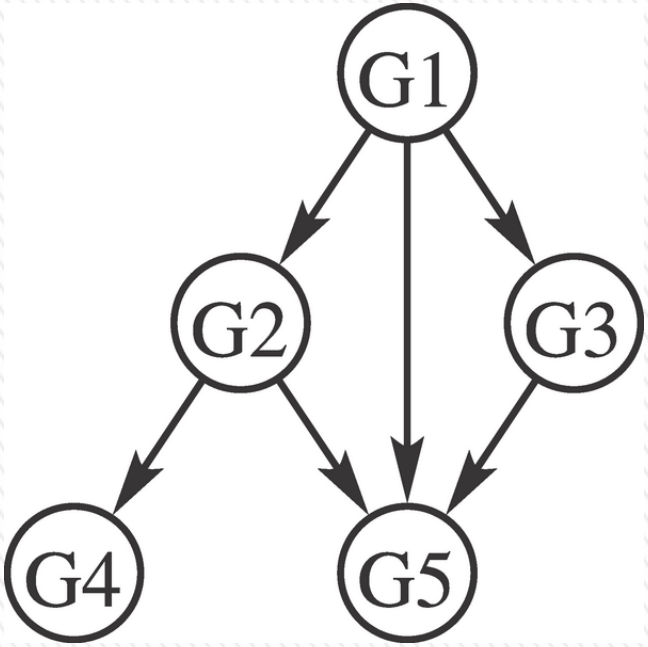




- GRN Reconstruction modeling techniques
  - Linear Model
  - **Bayesian Networks**
  - Differential Equations
  - Boolean Network
  - Neural Networks
  - **Hybrid models**

Bayesian Network (BN)

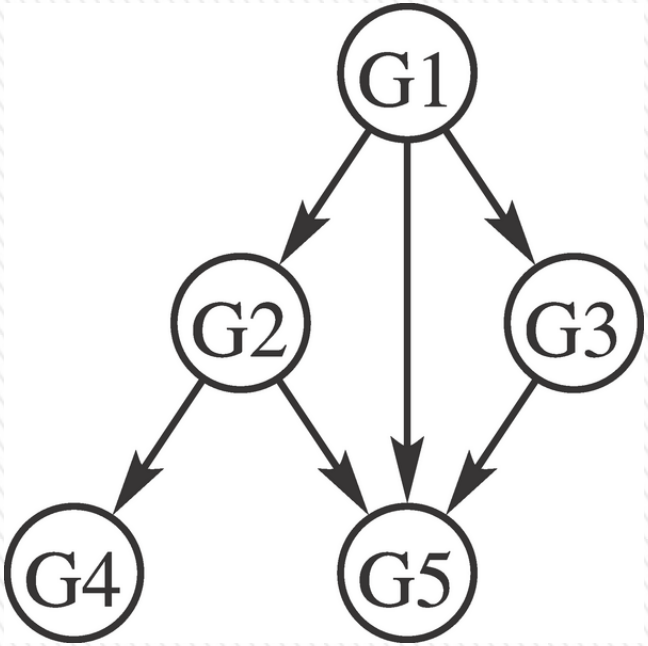
- A directed acyclic graph (DAG)
  - Nodes represent mRNA expression levels
  - Edges represent the probability of observing an expression value given the values of the parent nodes.
- The probability distribution for a gene depends only on its regulators (parents) in the network



Example: G4 and G5 share a common regulator G2, i.e., they are conditionally independent given G2.

Joint Probability distribution

- A directed acyclic graph (DAG)
  - Nodes represent mRNA expression levels
  - Edges represent the probability of observing an expression value given the values of the parent nodes.
- The probability distribution for a gene depends only on its regulators (parents) in the network.



$$p(G1, G2, G3, G4, G5) =$$

$$p(G1)\, p(G2|G1)\, p(G3|G1) p(G4|G2)\, p(G5|G1, G2, G3)$$

Constructing a Bayesian Network

- Variables (nodes in the graph)
- Add edges to the graph by computing conditional probabilities that characterize the distribution of states of each node given the state of its parents.
- The number of possible network structures grows exponentially with the number of nodes, so an exhaustive search of all possible structures to find the one best supported by the data is not feasible.

Dynamic Bayesian Network (DBN)

- DBN is a general state-space model to describe stochastic dynamic system
- Bayesian network with time-series to represent temporal dependencies.
- Cycles allowed in the graph
- Satisfying the Markovian condition:
  - The state of a system at time t depends only on its immediate past state at time t-1.

Time-Varying Dynamic Bayesian Network (TVDBN)

- TVDBN: recovering the directed time-varying network structure (or the locations of nonzero entries in A) rather than the exact edge values
- Linear dynamic (autoregressive) model: $X^t = A * X^{t-1} + e$

- the edges between variables X(t-1) and X(t): nonzero entries in the transition matrix A^t

- Matrix A:

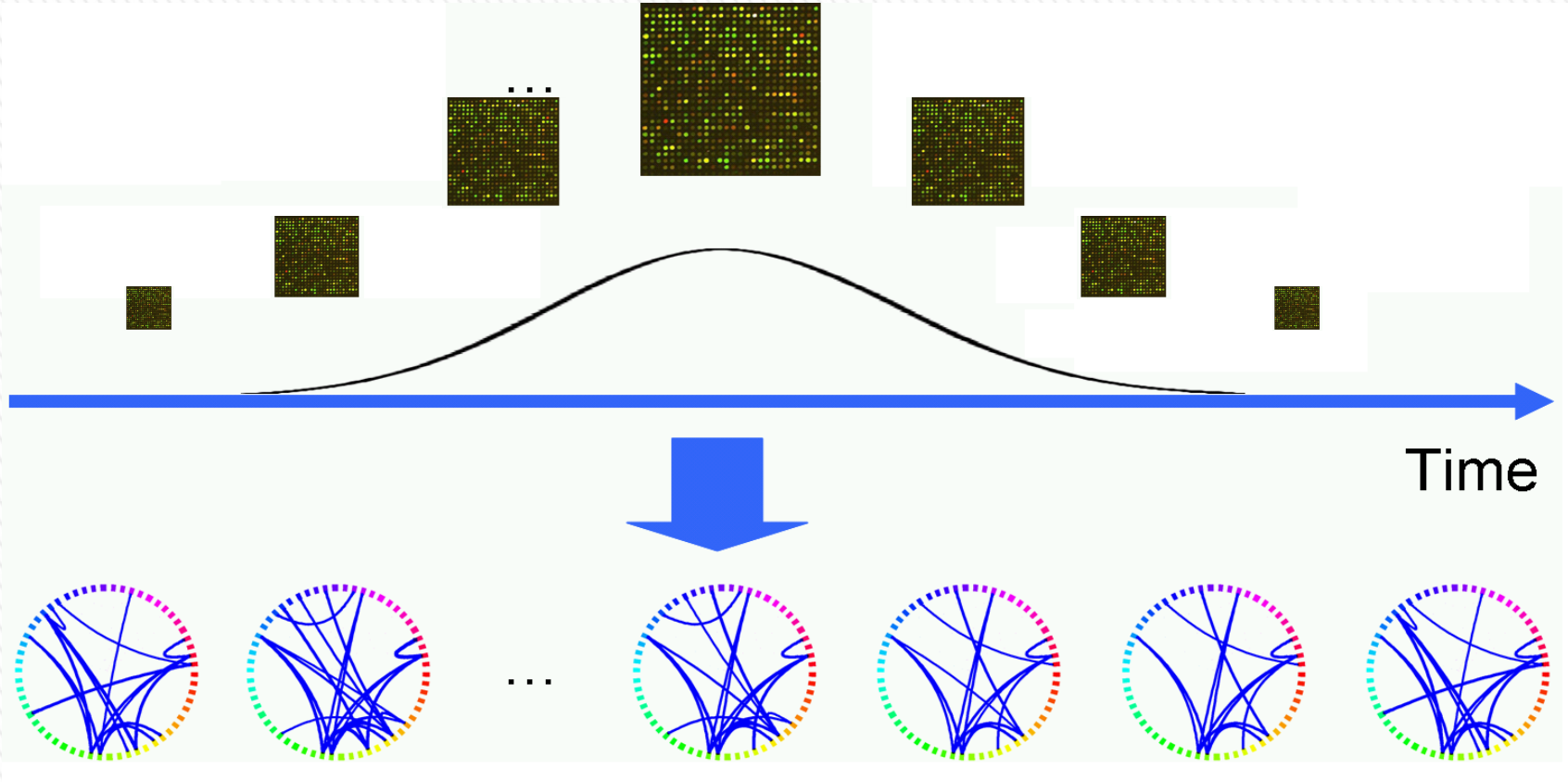
$$\hat{\boldsymbol{A}}_{i\cdot}^{t^\star} = \underset{\boldsymbol{A}_{i\cdot}^{t^\star} \in \mathbb{R}^{1\times n}}{\operatorname{argmin}} \frac{1}{T} \sum_{t=1}^{T} w^{t^\star}(t)(x_i^t - \boldsymbol{A}_{i\cdot}^{t^\star} \boldsymbol{x}^{t-1})^2 + \lambda \left\| \boldsymbol{A}_{i\cdot}^{t^\star} \right\|_1 ,$$

kernel reweighting scheme for aggregating observations, **time smoothness**

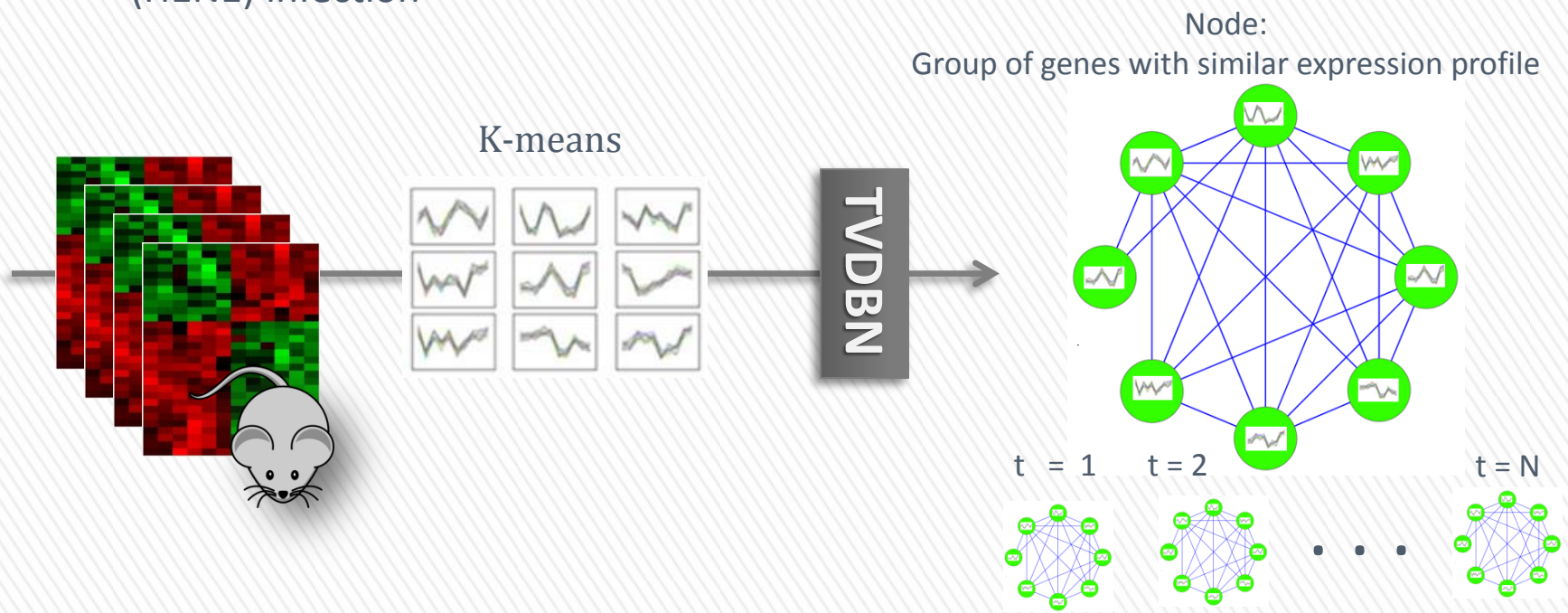
λ is a parameter for the l1-regularization term, controls sparsity, no overfitting

GRN Reconstruction with TVDBN

- TV-DBN elucidated the dynamic behavior of gene regulation circuitry and mapping the network structure transitions in response to pathogen stimuli.



Application: Dynamic GRN reconstruction in mice after influenza A (H1N1) infection

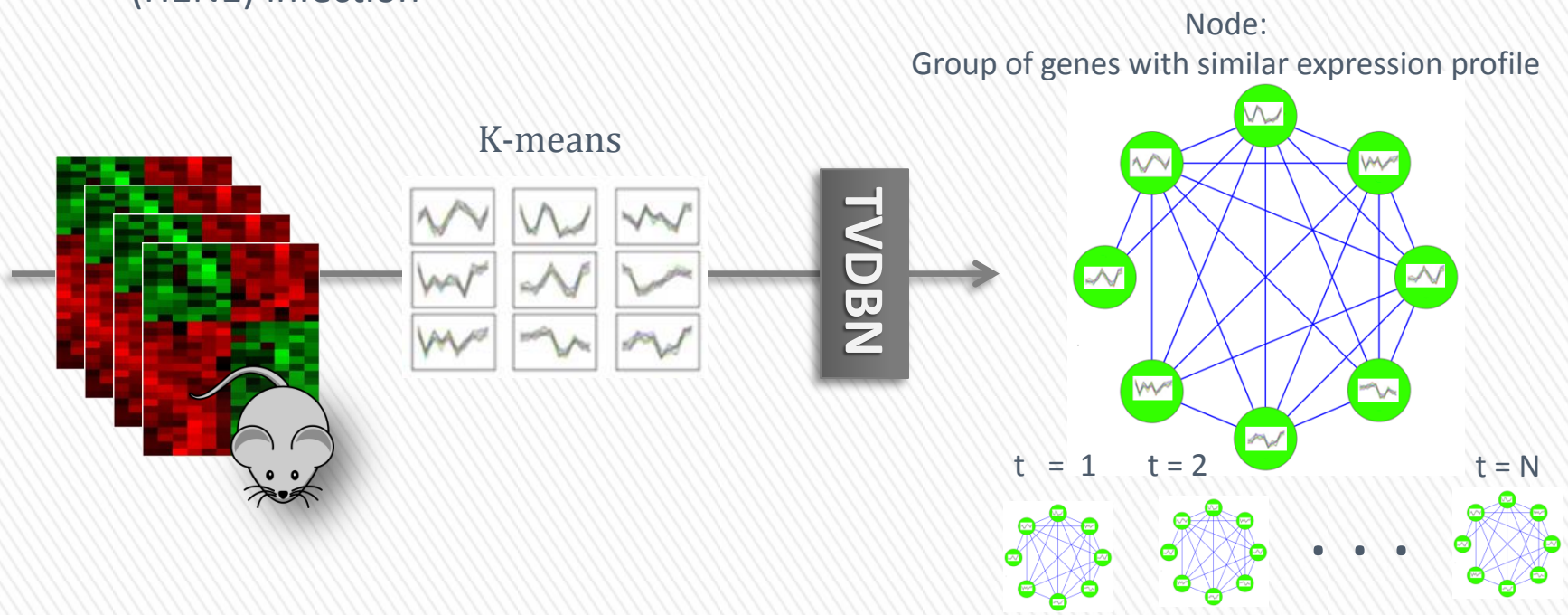


TVDBN based approach consists of four steps:

I. Data selection
II. Clustering for obtaining centroids,
III. Generation of Time Varying Dynamic Bayesian Networks based on the time series experimental expression profiles of cluster centroids and
IV. Evaluation of the resulting networks with respect to topological measures as well as with available biological knowledge.

K. Dimitrakopoulou, C. Tsimpouris, G. Papadopoulos, C. Pommerenke, E. Wilk, K. Sgarbas, K. Schughart, A. Bezerianos: "Dynamic gene network reconstruction from gene expression data in mice after Influenza A (H1N1) infection". Journal of Clinical Bioinformatics 2011

Application: Dynamic GRN reconstruction in mice after influenza A (H1N1) infection



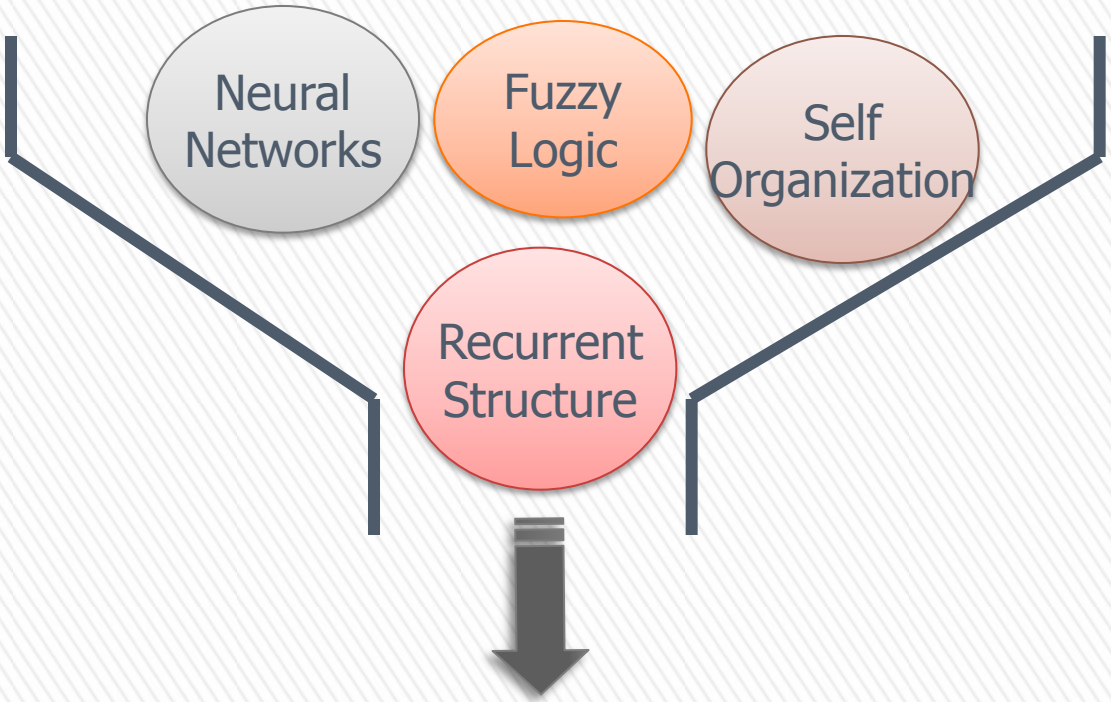
Results:

- We succeeded in detecting several gene-gene interactions known to be important in early host response.

K. Dimitrakopoulou, C. Tsimpouris, G. Papadopoulos, C. Pommerenke, E. Wilk, K. Sgarbas, K. Schughart, A. Bezerianos: "Dynamic gene network reconstruction from gene expression data in mice after Influenza A (H1N1) infection". Journal of Clinical Bioinformatics 2011

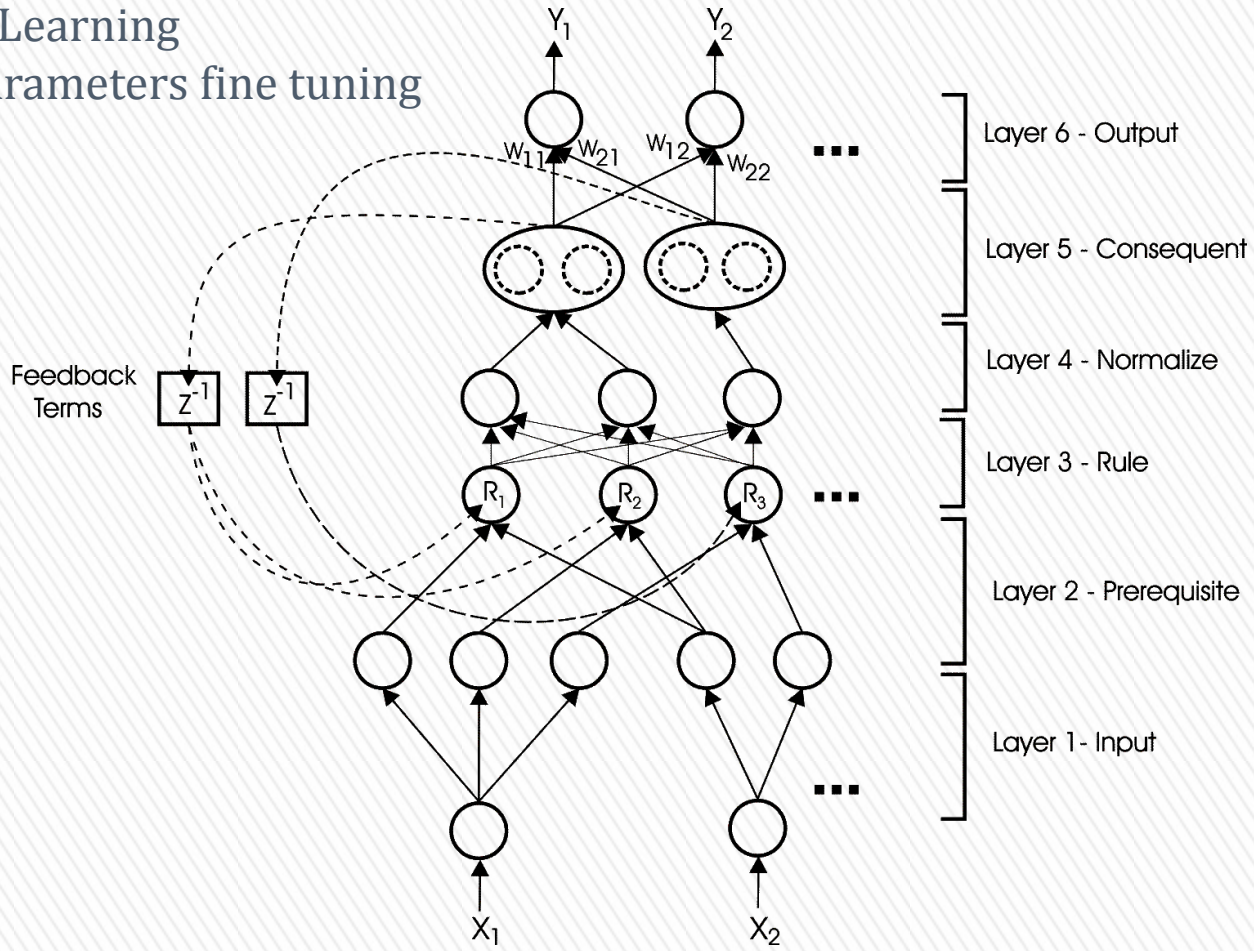
GRN Reconstruction with Hybrid Models

- An approach for inferring the complex causal relationships among genes from microarray experimental data based on a recurrent neuro-fuzzy method
- Extracts information on the gene interactions in a highly interpretable form (fuzzy rules) and
- Takes into account dynamical aspects of genes regulation through its recurrent structure



GRN Reconstruction with NFRN

- Phase 1: Structure Learning
  - Segmentation of input-output space
  - Automatic Construction of Fuzzy Rules
  - Regulation of recurrent links
  - Determining parameters (fuzzy sets)
- Phase 2: Parameters Learning
  - Algorithm for parameters fine tuning



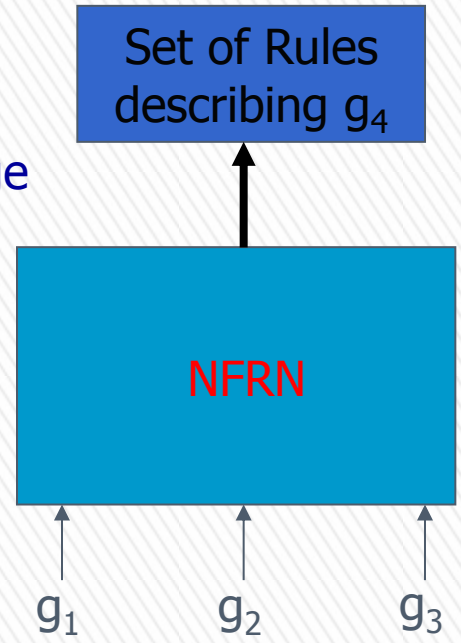
Fuzzy Rules Describing Gene Interactions

Example of Rules:

If g_1 is Low and g_2 is High and g_3 is Average → g_4 is Low

If g_1 is High and g_2 is High and g_3 is Average → g_4 is Average

If g_1 is Low and g_2 is High and g_3 is High → g_4 is Low



- *Maraziotis, I. A., Dragomir, A., & Bezerianos, A. (2007). Gene networks reconstruction and time-series prediction from microarray data using recurrent neural fuzzy networks. Systems Biology, IET, 1(1), 41-50.*
- *Bezerianos, A., & Maraziotis, I. A. (2008). Computational models reconstruct gene regulatory networks. Molecular Biosystems, 4(10), 993-1000.*

Moving forward… the wisdom of crowds

- GRN Inference problem
  - plethora of algorithms available in recent literature
- Idea:
  - intersecting the networks inferred by several algorithms (the concept is known as ‘wisdom of the crowd’) and retaining the overlapping interactions, rather than comparing all algorithms in terms of performance and selecting the network of the superior for subsequent analysis
- The idea behind this choice is that we expect unanimously voted interactions to be more reliable and realistic

Methodology

Find Differential expressed Genes (DEG)

Algorithm ENFRN

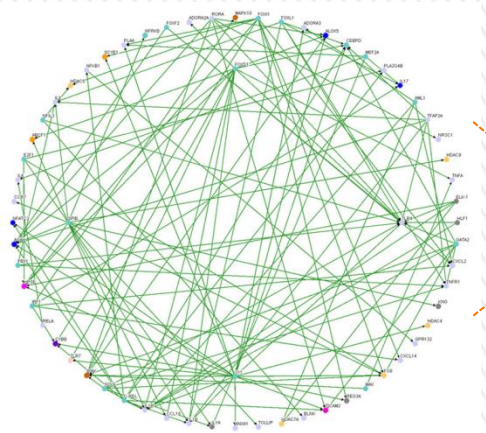
Algorithm AIJO

Algorithm TD-ARACNE

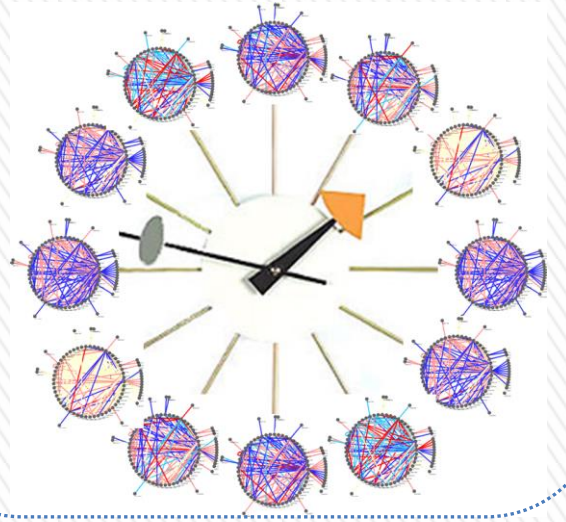
Algorithm TV-DBN

Algorithm KELLER

Shared Interactions



Kinetic Model

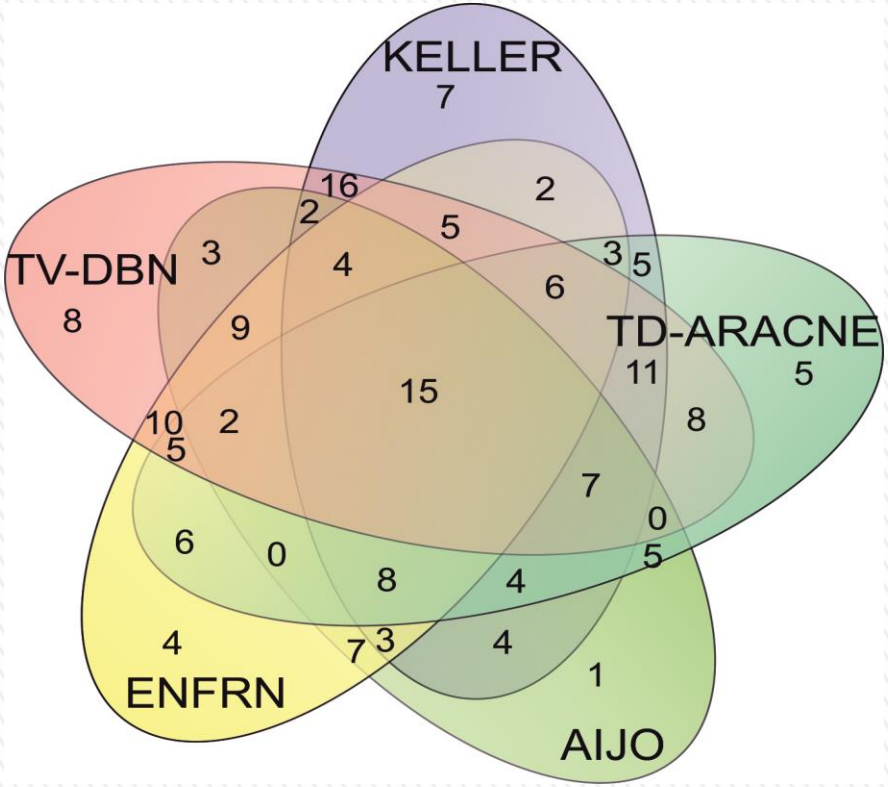


Dimitrakopoulou, K., Dimitrakopoulos, G. N., Wilk, E., Tsimpouris, C., Sgarbas, K. N., Schughart, K., & Bezerianos, A. (2014). Influenza A Immunomics and Public Health Omics: The Dynamic Pathway Interplay in Host Response to H1N1 Infection. Omics: a journal of integrative biology, 18(3), 167-183.

Application in Influenza H1N1

Depicting immune response mechanisms

Results



Venn diagram with shared interactions from 5 GRN methods

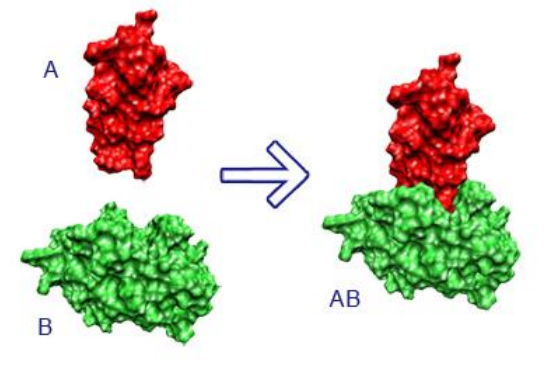
Dimitrakopoulou, K., Dimitrakopoulos, G. N., Wilk, E., Tsimpouris, C., Sgarbas, K. N., Schughart, K., & Bezerianos, A. (2014). Influenza A Immunomics and Public Health Omics: The Dynamic Pathway Interplay in Host Response to H1N1 Infection. Omics: a journal of integrative biology, 18(3), 167-183.

Introduction

I. Basic Concepts
II. Introduction to Biology
III. Introduction to Biological Networks
IV. Gene Regulatory Networks
V. Protein-Protein Interactions Network
VI. Cell Signaling Networks (Pathway)

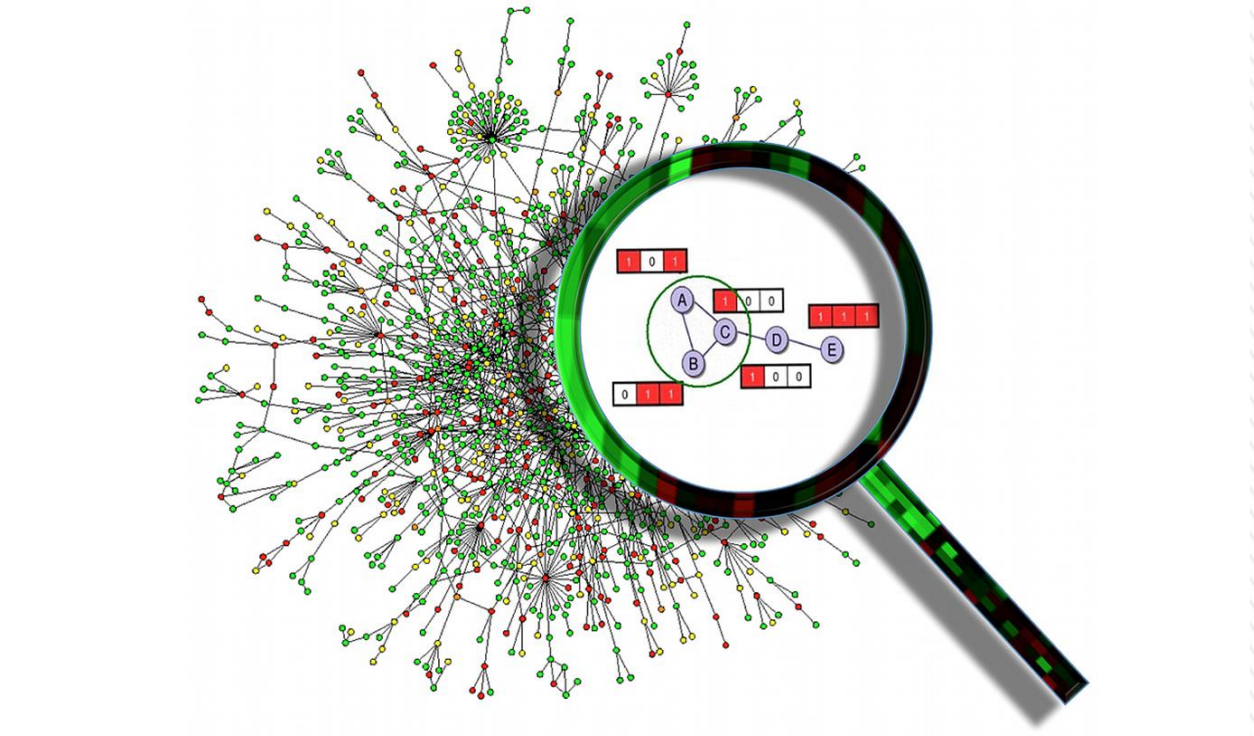
Protein - Protein Interaction networks (PPI)

- Physical interactions between proteins are an important mechanism behind many cellular processes
- A protein-protein interaction (PPI) usually refers to a physical interaction, i.e., binding between proteins
- Can be other associations of proteins such as functional interactions – e.g. synthetic lethality

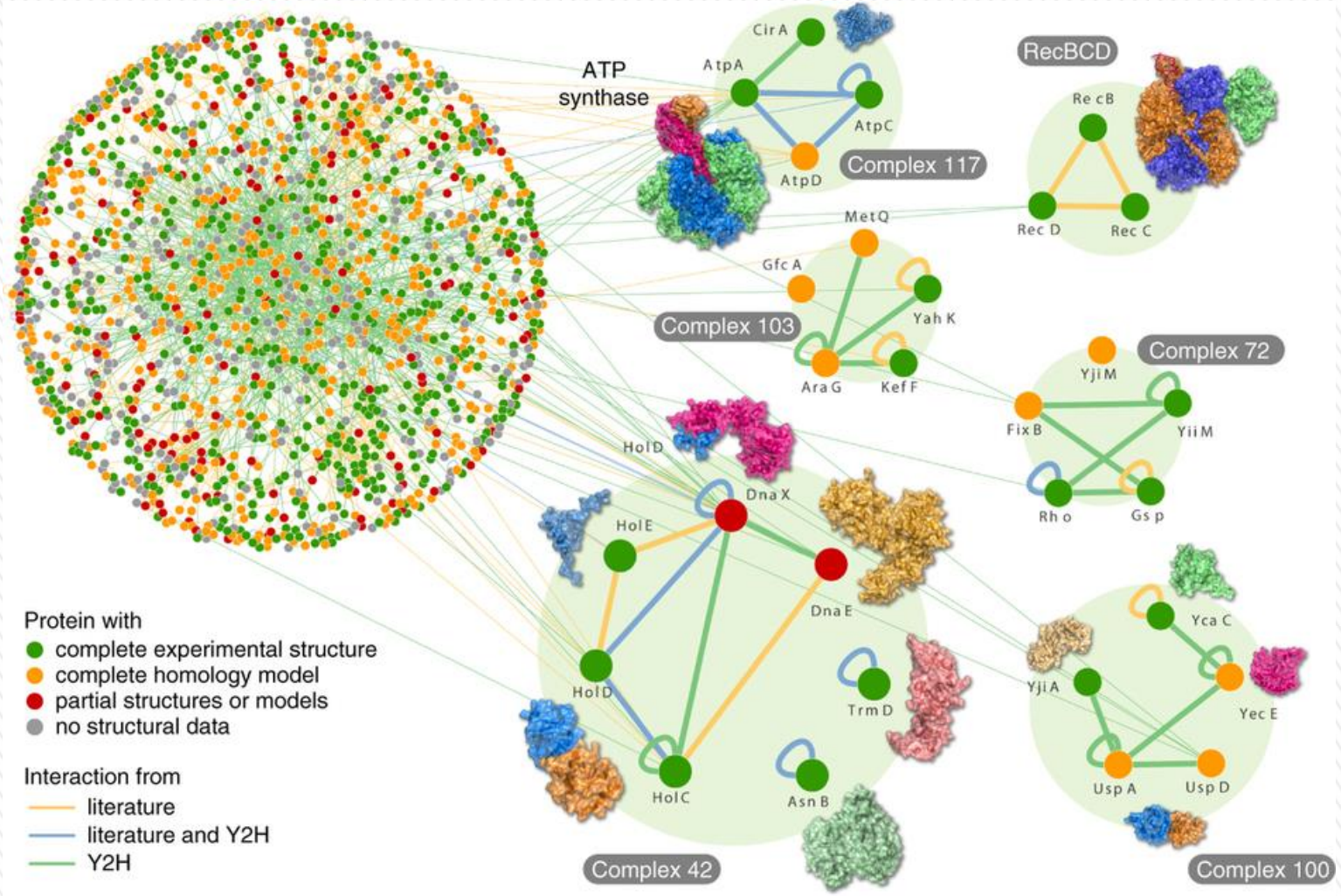


Protein - Protein Interaction networks (PPI)

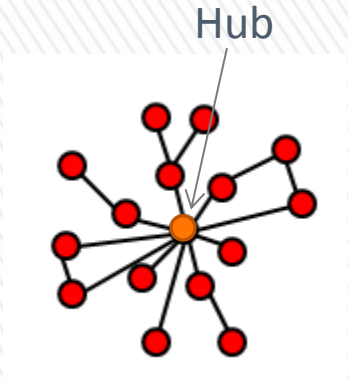
- PPIs are very important for structure and function of a cell:
  - Play a role in many diseases (e.g., cancer)
  - Can be stable interactions forming a protein complex
- Identifying functional modules in protein-protein interaction (PPI) network
  - Biomarkers are encoded as subnetworks of interacting proteins (within a larger PPI network)



The binary protein-protein interaction landscape of *Escherichia coli*

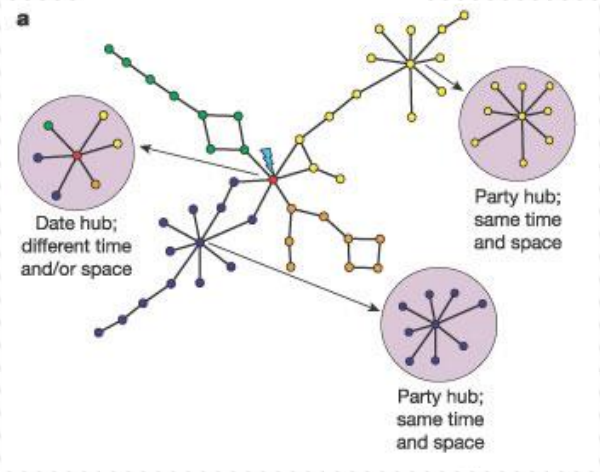


Network properties of PPIs



HUBS

Highly connected nodes (proteins)



PARTY HUB

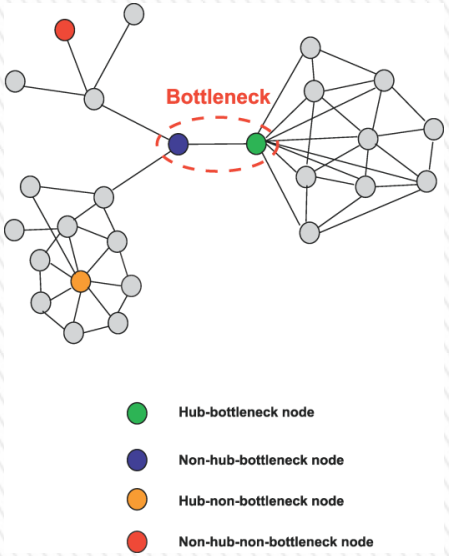
hubs whose expression is correlated with its interaction partners

Date Hubs

Hubs that do not exhibit such a correlation and appear to connect different functional modules

Bottleneck

- key connector nodes with surprising functional and dynamic properties
- correspond to the dynamic components of the interaction network

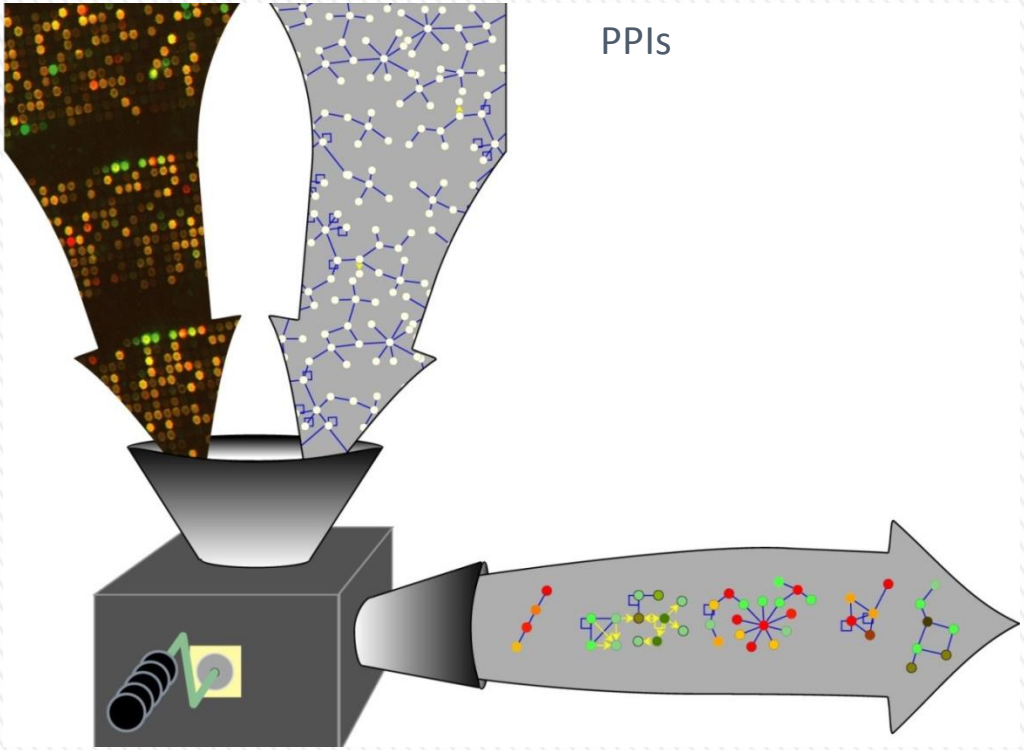


INTEGROMICS: Integrating Omics Data with PPI Networks

Why?

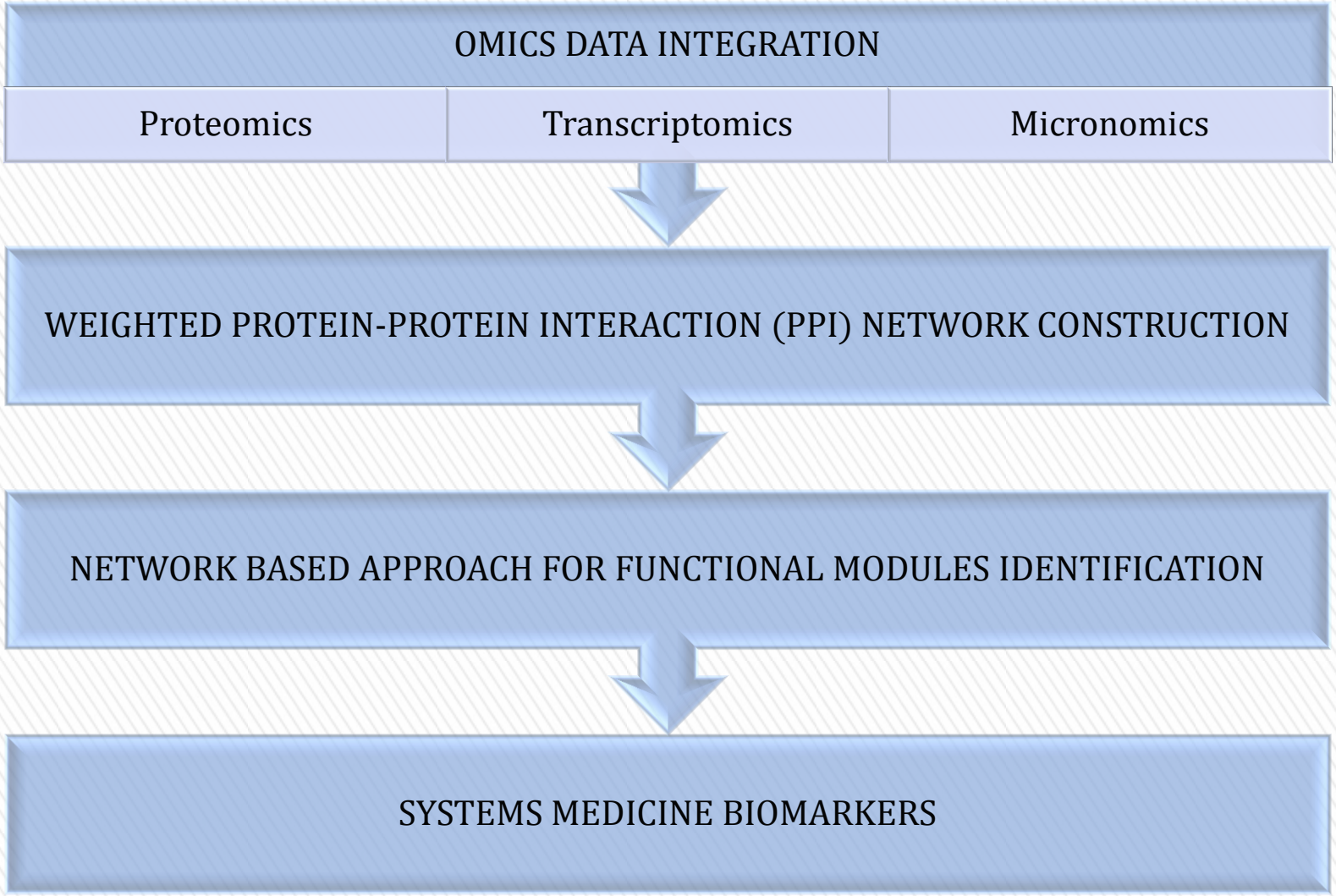
- PPI Networks have false positive interactions and lack of temporal information
- Integration serves as a means for capturing multiple aspects of cellular processes
- The integration and of multiple omics data offers a more realistic view of the mechanisms under investigation

Gene expressions



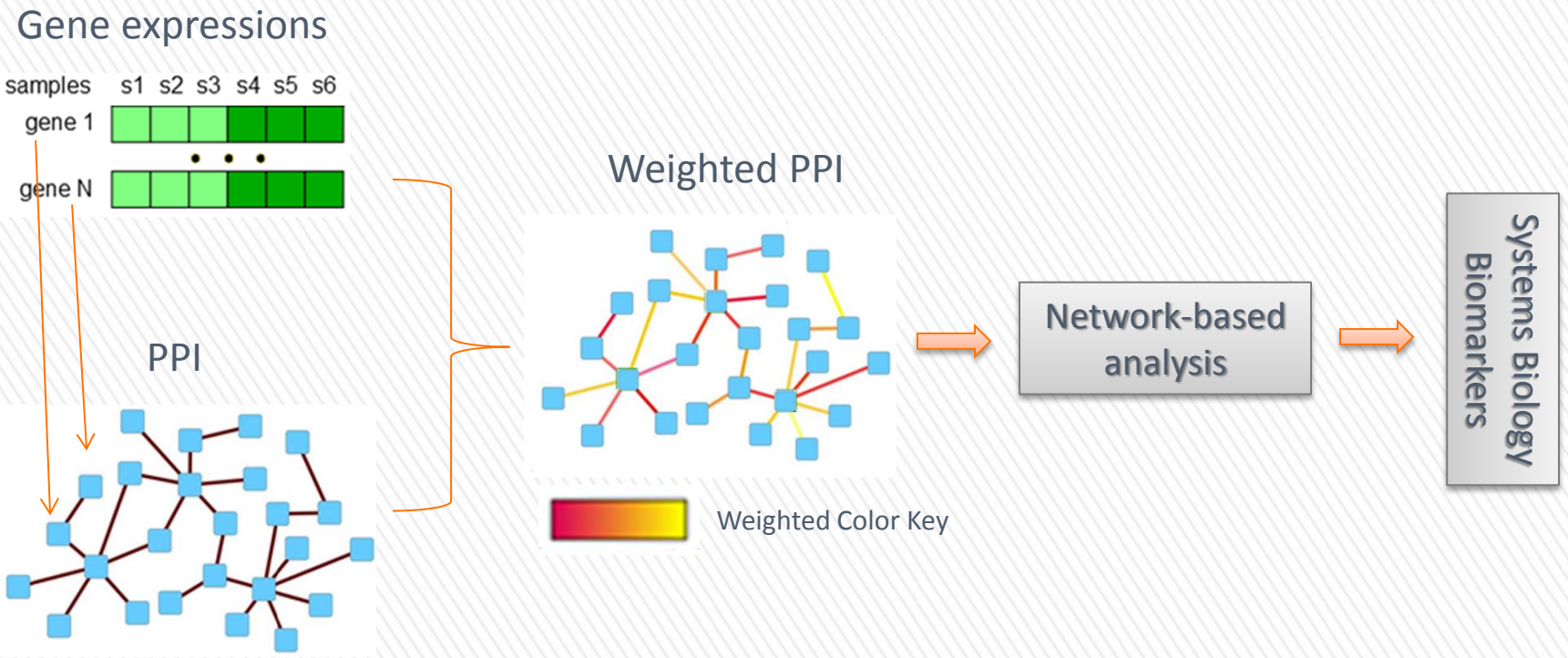
PPIs

General Framework of Network-based INTEGROMICS approach



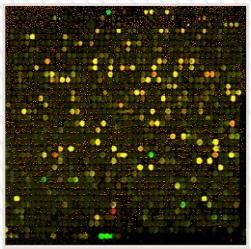
Network-based Integromics approach – An example

- gene expression profiling techniques record mRNA abundance
- Basic assumption
  - mRNA abundance ~= protein abundance
- In silico assumption
  - Gene = protein

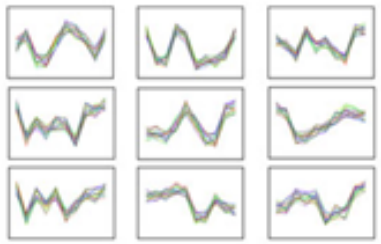


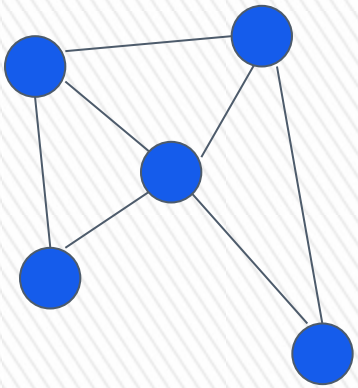
Module-based analysis in integrated PPI Graph

- We proposed a method that corroborates the integration of protein interaction and microarray data via the discovery of biologically valid functional modules.
- Data Integration:

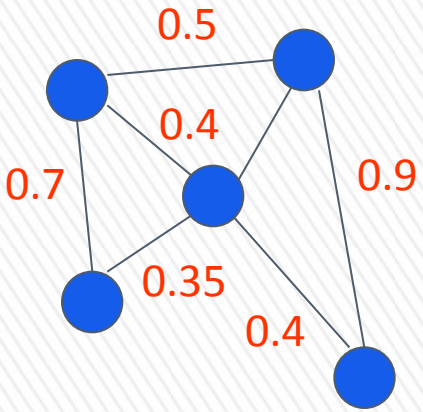


Fuzzy c-means clustering





$$W(x,y) = n_1\left(\left\|x - K_x\right\|^2 + \left\|y - K_y\right\|^2\right) + n_2\left\|K_x - K_y\right\|^2$$



Detect Module from Seed Protein (DMSP) Operation

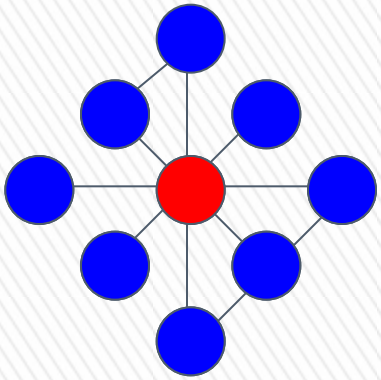
'seed' Protein (s)

Maraziotis, I. A., Dimitrakopoulou, K., & Bezerianos, A. (2007). Growing functional modules from a seed protein via integration of protein interaction and gene expression data. Bmc Bioinformatics, 8(1), 408.

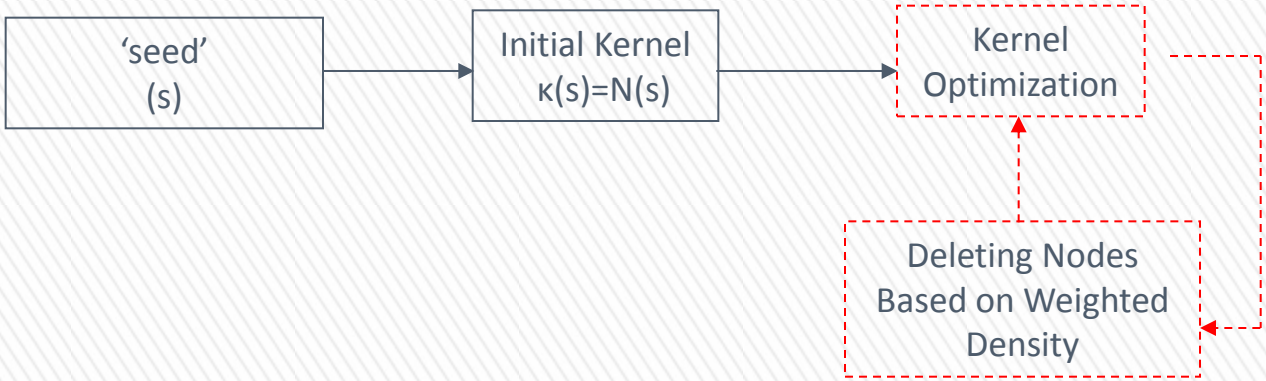
DMSP Operation

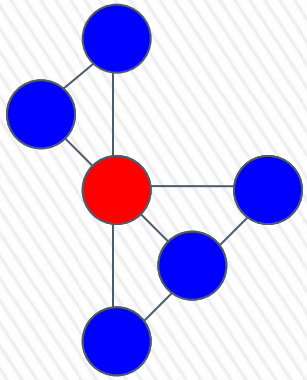
‘seed’ Protein (s)

Initial Kernel κ(s)=N(s)

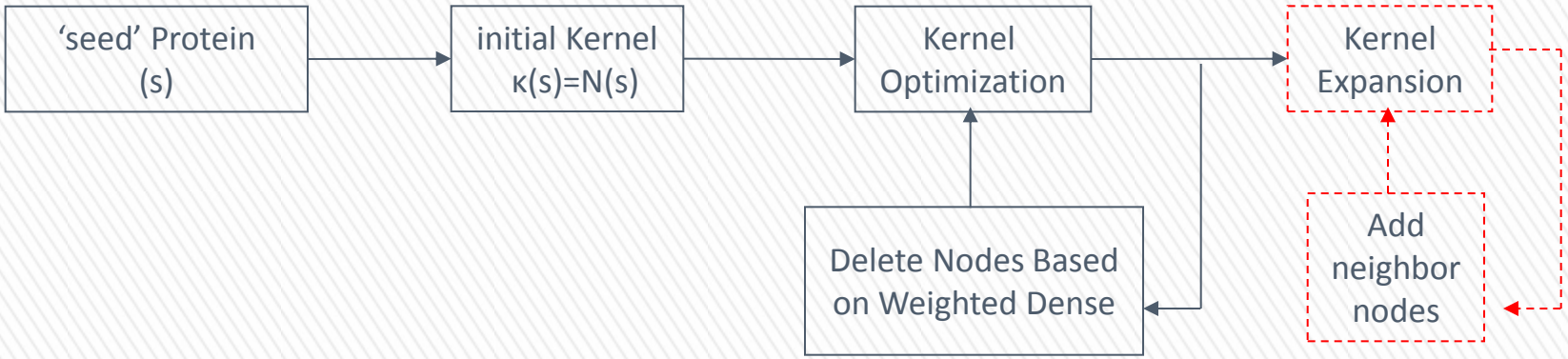


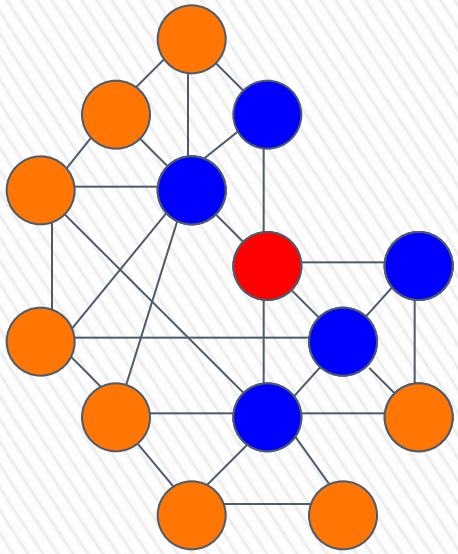
DMSP Operation



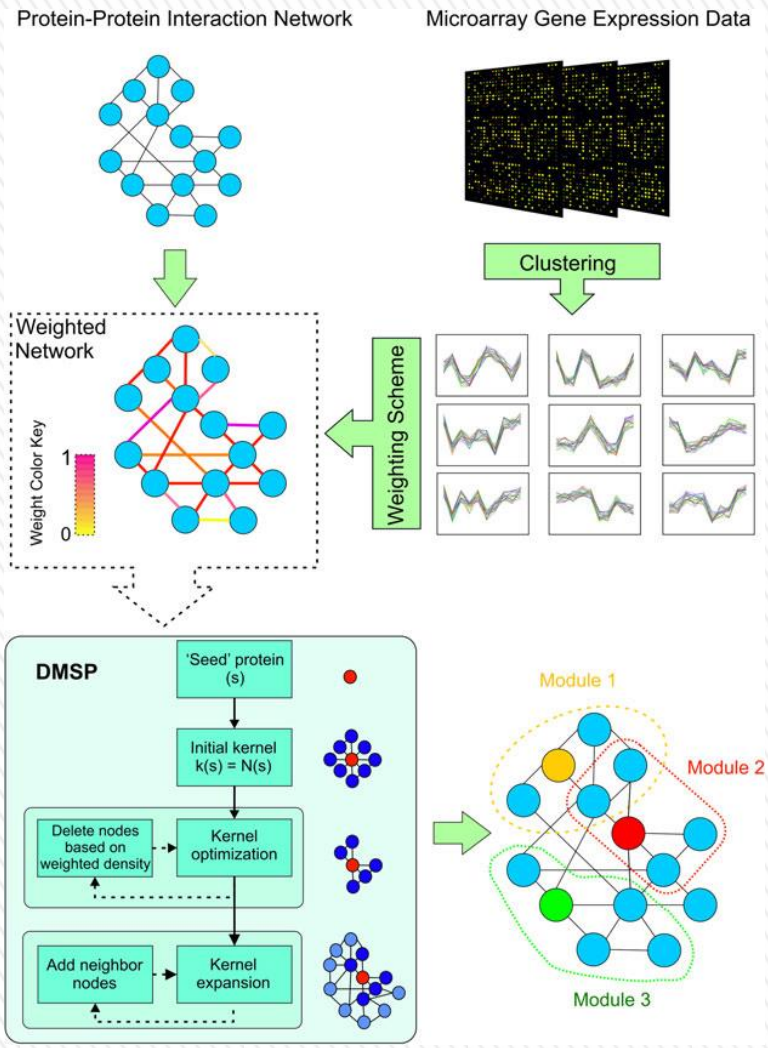


DMSP Operation





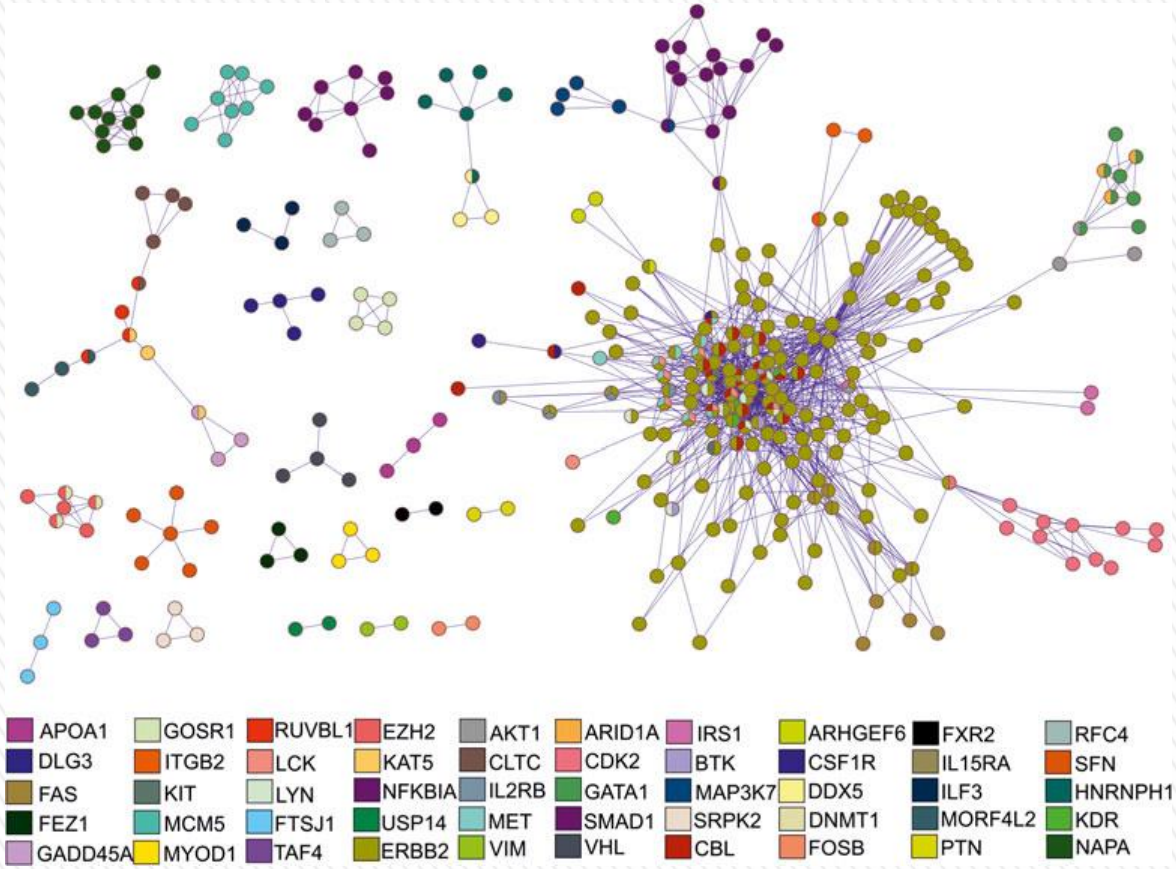
Large scale Integromics approach in breast cancer treatment with tamoxifen



- **First**, the gene expression profiles are clustered with k-means algorithm.
- **Second**, a weighting scheme, based on the clustering result, is employed, resulting in the construction of a weighted protein interaction graph.
- **Finally**, DMSP is applied onto the composite graph, which identifies functional modules
  - These modules are potential biomarkers for breast cancer treatments

Dimitrakopoulou, K., Dimitrakopoulos, G. N., Sgarbas, K. N., & Bezerianos, A. (2014). Tamoxifen integromics and personalized medicine: Dynamic modular transformations underpinning response to tamoxifen in breast cancer treatment. Omics: a journal of integrative biology, 18(1), 15-33.

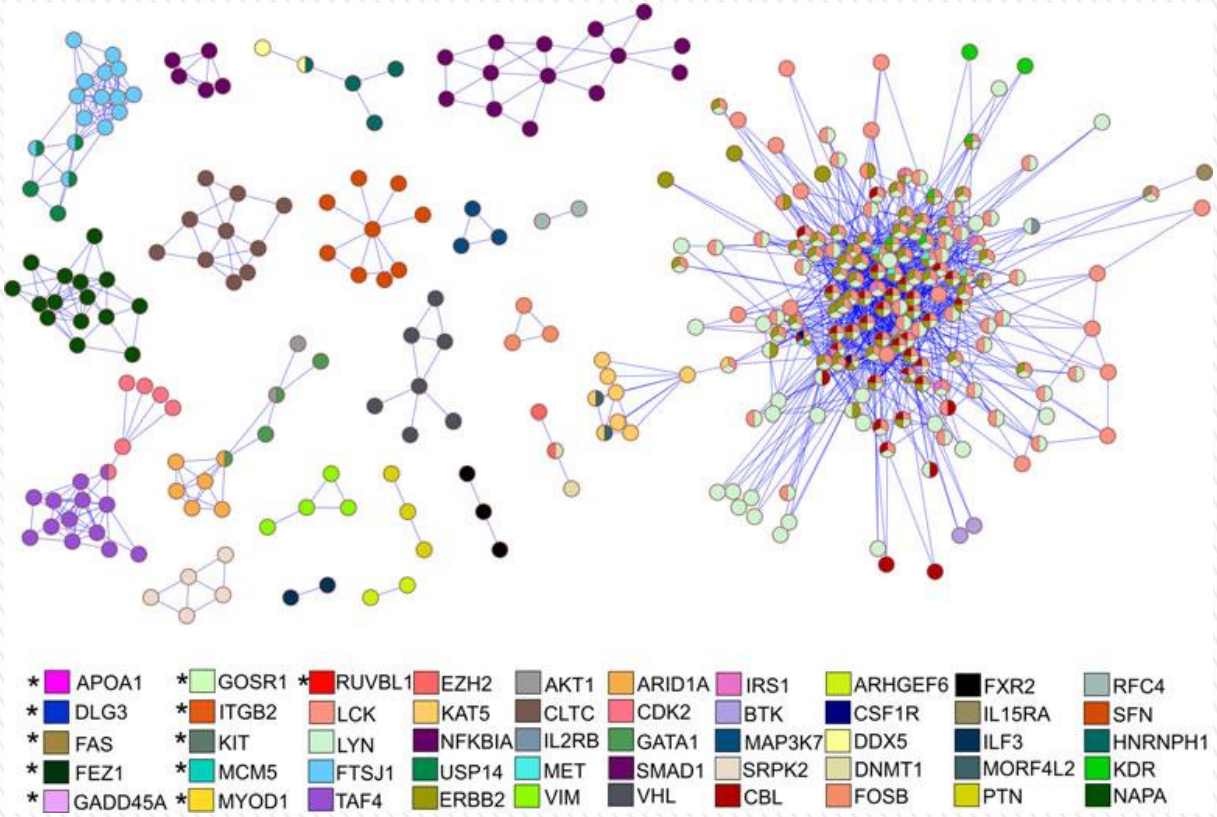
Results – Estradiol Network (Control)



Network visualization of the 50 modules in estradiol graph.

Dimitrakopoulou, K., Dimitrakopoulos, G. N., Sgarbas, K. N., & Bezerianos, A. (2014). Tamoxifen integromics and personalized medicine: Dynamic modular transformations underpinning response to tamoxifen in breast cancer treatment. Omics: a journal of integrative biology, 18(1), 15-33.

Results –Tamoxifen Network (Treatment)



Network visualization of the 50 modules in tamoxifen graph.
it is obvious that severe modular transformations occurred after tamoxifen administration

Dimitrakopoulou, K., Dimitrakopoulos, G. N., Sgarbas, K. N., & Bezerianos, A. (2014). Tamoxifen integromics and personalized medicine: Dynamic modular transformations underpinning response to tamoxifen in breast cancer treatment. Omics: a journal of integrative biology, 18(1), 15-33.

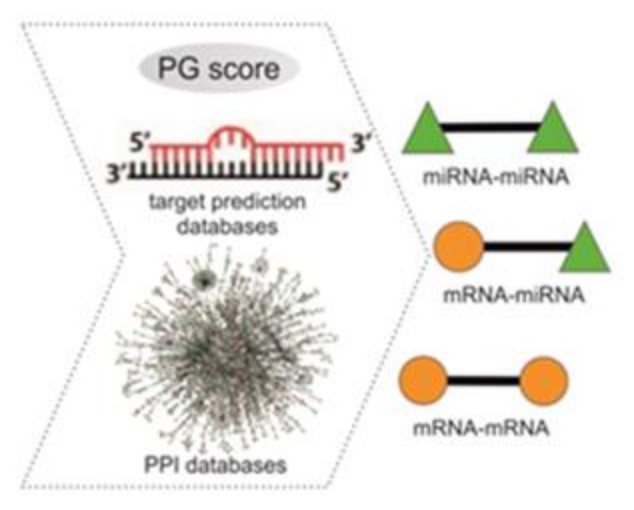
Integromics Approach:
Gene expressions Data + PPIs + incorporate miRNAs (???)

Necessity

- The role of microRNAs in complex diseases has recently emerged and is far from known.
- Goal: To emerge the synergistic effect of microRNAs in complex diseases

Design

- An integromics network-based approach that combines omics data (transciptomics - proteomics - micronomics) from complex diseases in the form of composite network.
- Construction of a Multilayer Large Scale Omics Network (MLSON)
  - 2 types of nodes (mRNA & miRNA)
  - 3 types of relations (mRNA-mRNA, mRNA-miRNA, miRNA-miRNA)
- Meta-analysis of the final network provide robust disease markers that could serve as potential drug targets.



STEP I - The construction of Multilayer Large Scale Omics Network (MLSON)

Interaction Data (three types of interactions)

- **Proteome (mRNA-mRNA relations):**
  - By combining data from multiple well known PPI databases (BioGRID, IntAct, MINT, DIP)
- **Micronome (mRNA-miRNA relations)**
  - By combing the results from six target-prediction databases – miRGEN, miRTarBase, TarBase, miRecords, miRWalk and StarBase.

Interaction Data (three types of interactions)

- Micronome (miRNA-miRNA relations)
  - We utilized metric 'PG score', which identifies functional relationships between miRNAs.
  - Based on the hypothesis that their co-regulating targets are highly enriched in the same Gene Ontology (GO) biological process terms
  - For a given miRNA pair A and B, the probability PG_i in the GO term i is calculated as:

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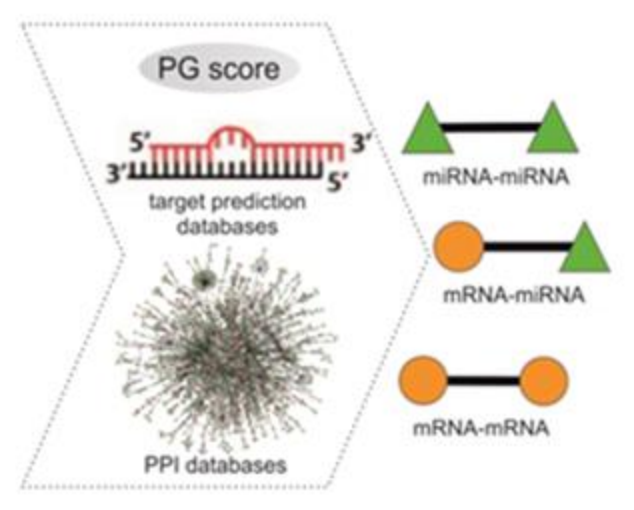
$$PG_i = 1 - F(x|N, K_i, M) = \sum_{t=0}^{x} \frac{\binom{K_i}{t}\binom{N-K_i}{M-t}}{\binom{N}{M}}$$



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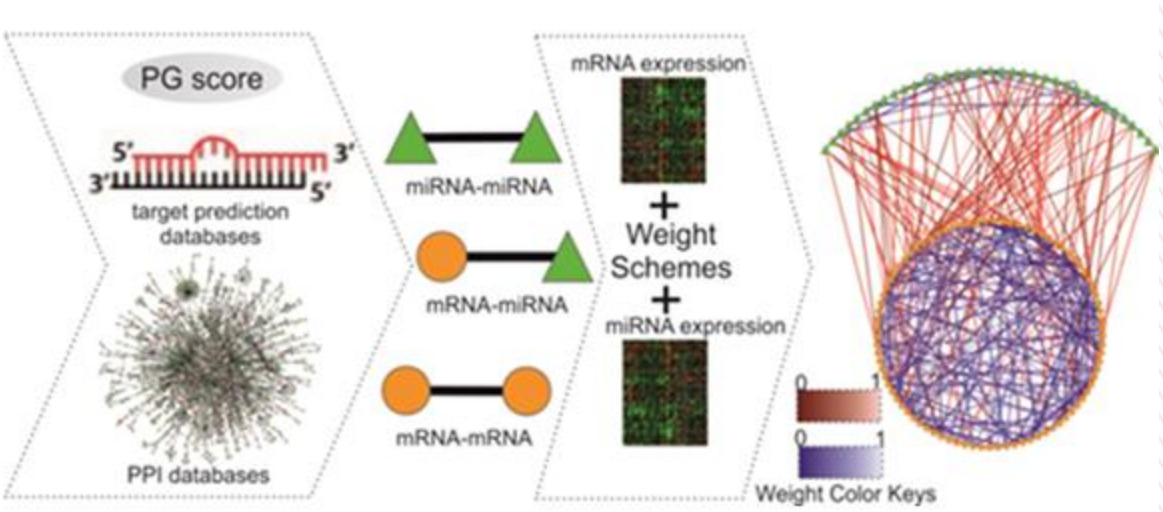
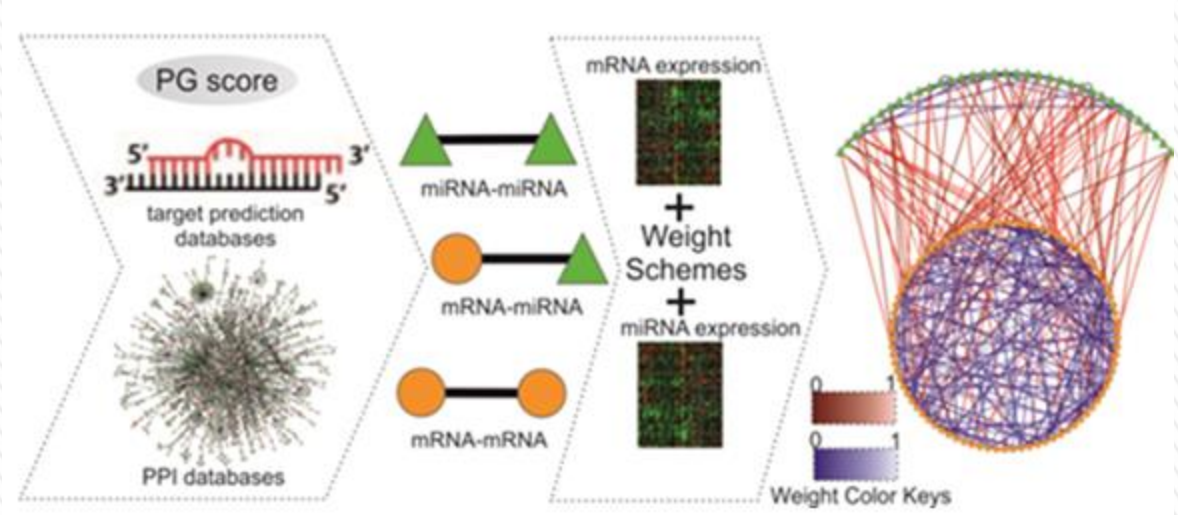
- $i = 1,2,\ldots,I$: *the number of all target*
- K_i : *the total number of genes that are annotated in the GO term i and targeted by miRNAs,*
- M : *is the size of* $A \cap B$,
- x: *is the number of targets in* $A \cap B$ *that are also annotated to term i*



Step II

STEP I - Weighting Schemes of MLSON

- **mRNA-mRNA/ miRNA-miRNA interactions**
  - Goal: to capture the significant expression changes during the transition from 2 states.
  - we utilized a discriminative score (DS), as in previous work, in order ……



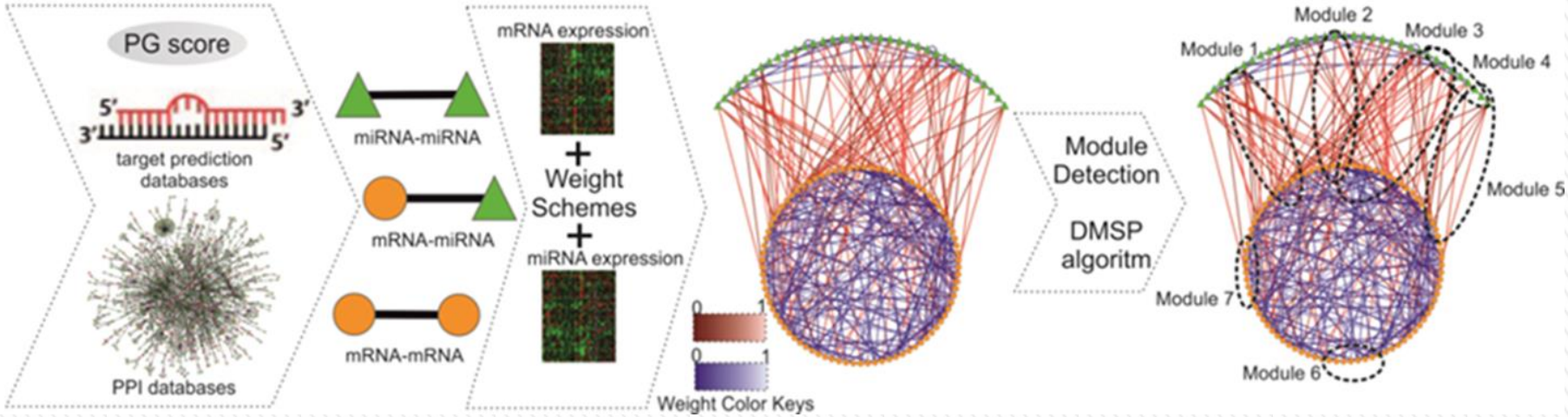
Step II

STEP I I- Weighting Schemes of MLSON

- **mRNA-miRNA interactions**
  - **Goal**: to capture both the correlation and anti-correlation patterns between mRNA and miRNA nodes and the simultaneous differentiation from young to old state
  - We utilized an efficient weighting scheme, called interaction information
  - For three variables X, Y, Z, three-way interaction information I is defined as

$$I(X;Y;Z) = CMI(X;Y|Z) - MI(X;Y)$$

X, Y : the expression of each pair of mRNA-miRNA
Z : the class (1 for young, 2 for old state).
MI, CMI : Mutual Information and Conditional MI respectively



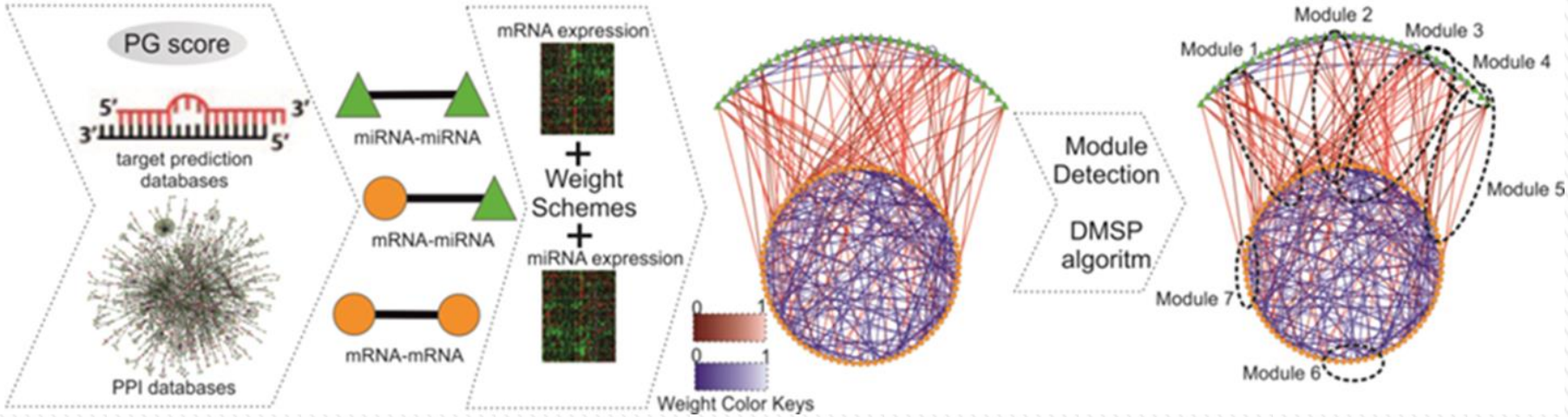
Construction of MLSON Network

Weighting of MLSON Network

Modular meta-analysis

STEP III - Apply DMSP

- The resulting weighted MLSON network, is used as input in the Detect Module from Seed Protein (DMSP) Algorithm, in order to find functional modules that alter during two different states (young and old state)



Construction of MLSON Network

Weighting of MLSON Network

Modular meta-analysis

STEP IV – Meta-analysis of modules

- We searched for modules with high node overlap across multiple independent datasets
  - we computed the node overlap ratio defined as

$$NOR(M_i, M_j) = 2 * \frac{M_i \cap M_j}{M_i + M_j}$$

Where M_i, M_j : the compared modules derived from the same seed protein in the two experiments respectively.

Application in heart aging

Step I

- The construction of Multilayer Large Scale Omics Network (**MLSON**)
  - 2 types of nodes (mRNA & miRNA)
  - 3 types of relations (mRNA-mRNA, mRNA-miRNA, miRNA-miRNA)

Step II

- The design of two adapted weighting schemes applied on the interactions of MLSON Network

Step III

- The application of a module detecting algorithm in order to identify groups of nodes that alter during aging

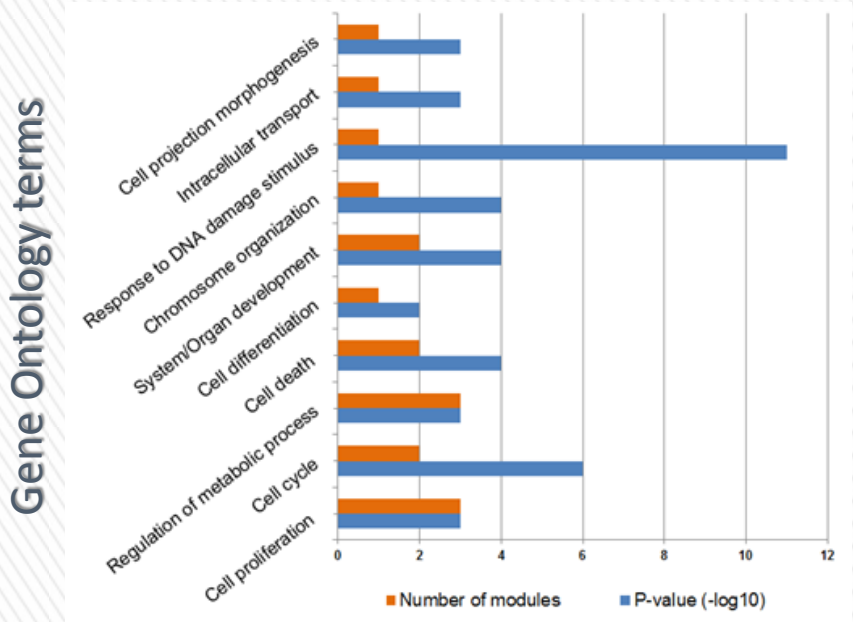
Step IV

- Modular meta-analysis in order to identify cardiac longevity associated modules irrespective of gender factor.

Dimitrakopoulou, K., Vrahatis, A. G., Dimitrakopoulos, G. N., & Bezerianos, A. (2014, January). Aging Integromics: Module-Based Markers of Heart Aging from Multi-omics Data. In The 15th International Conference on Biomedical Engineering (pp. 104-107). Springer International Publishing.

Results – Gene Ontology analysis

- Gene Ontology enrichment analysis of the final heart modular longevity-associated markers.
- Fully supported from Literature



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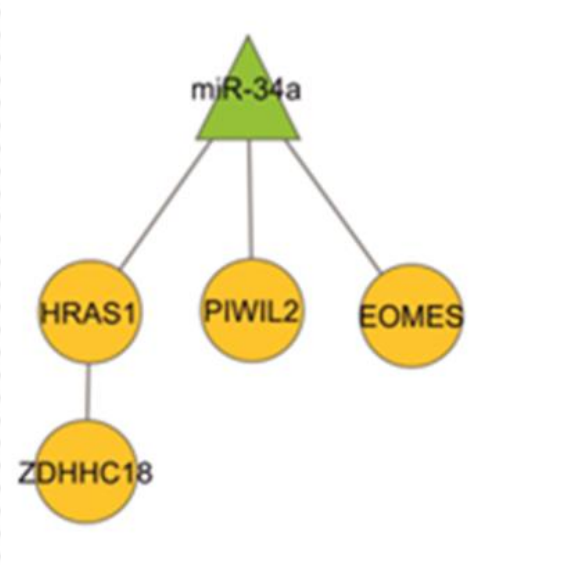
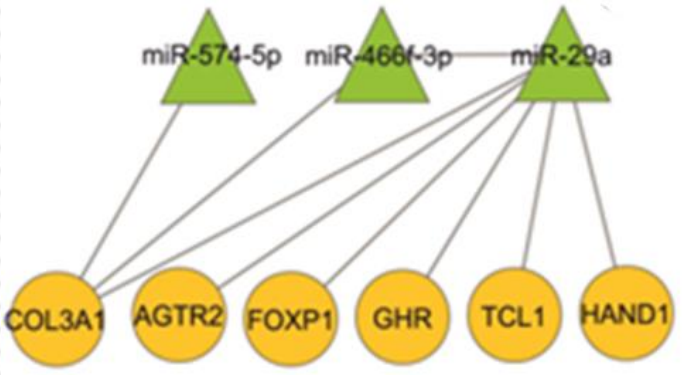
Results – Multilevel modular markers of cardiac aging

- Two characteristic modular markers identified by our integromics approach
- Individual cardiac biomarkers supported by recent literature are updated through the perspective of multilayer communities of molecules





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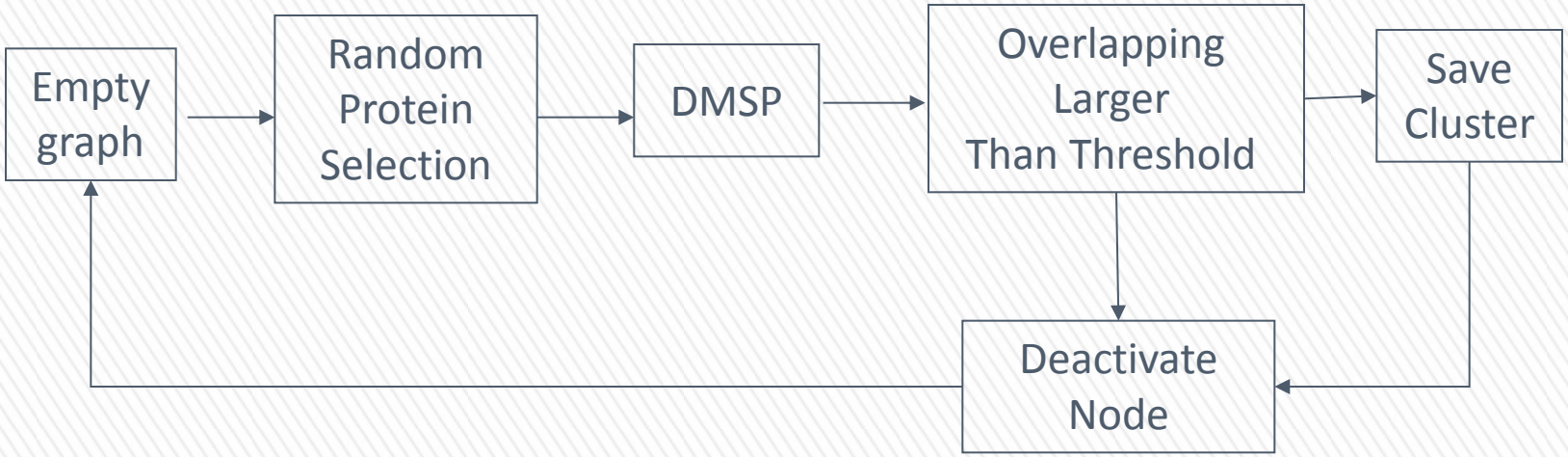
Detect Overlapping Modules (DetMod)

- Evolutionary step of DMSP
- Captures important features of proteins i.e. participate in multiple biological processes and thus in functional modules (*Disadvantage of DMSP*)
- Combines DMSP with a node and module scoring strategy that allows functional module overlapping thus capturing inter-module cross-talk

Maraziotis, I. A., Dimitrakopoulou, K., & Bezerianos, A. (2008). An in silico method for detecting overlapping functional modules from composite biological networks. BMC Systems Biology, 2(1), 93.

Detect Overlapping Modules (DetMod)

- DMSP is applied on every node
- Each newly constructed module is checked in terms of overlap with the rest of the modules that have been previously created.
- If this overlapping degree is above a certain threshold then the module is discarded
- The derived modules are further examined in order to determine if merging is plausible



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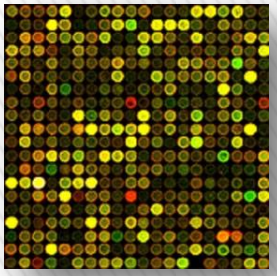
Meta-Analysis Network-Based approaches

1 experiment



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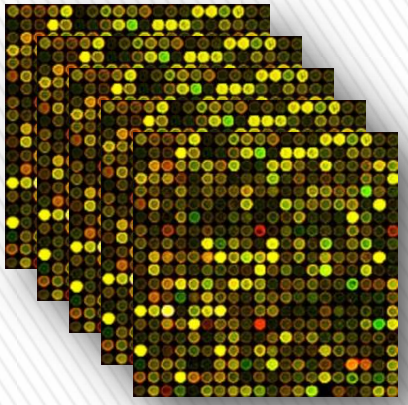
PPI

Network-Based Approach

Modular Analysis

Meta-analyses of gene expression profiles integrating multiple microarray studies have been particularly useful to identify conserved genetic signatures of complex diseases

Multiple experiments



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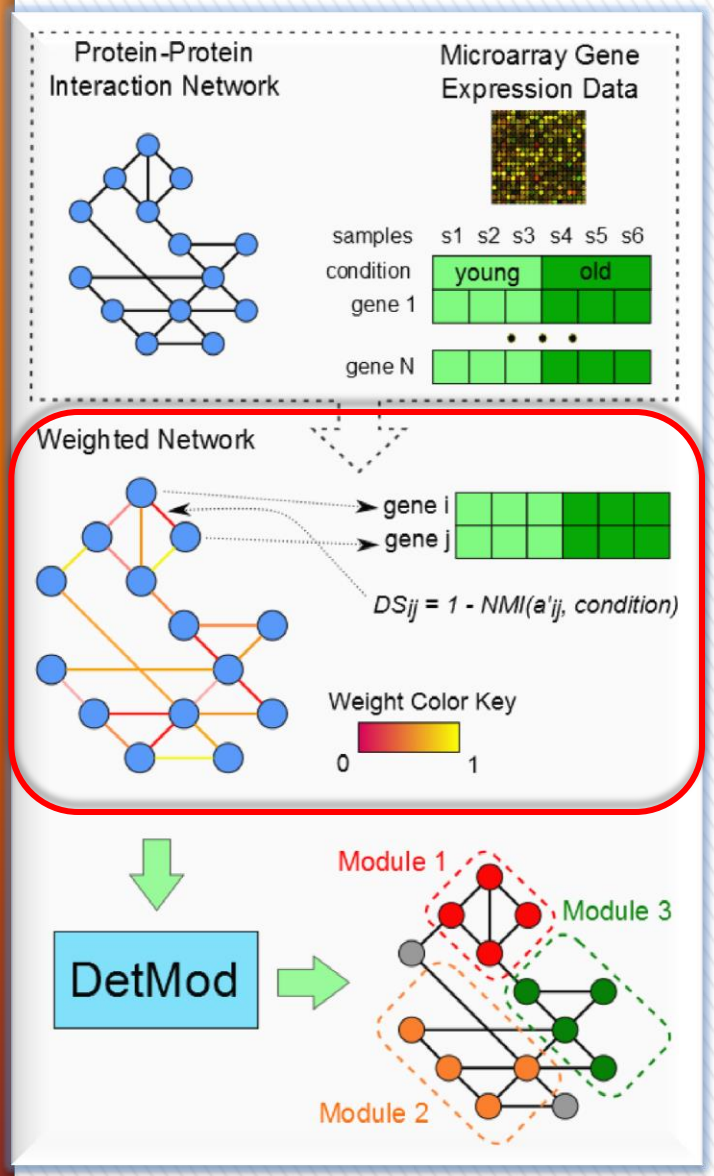
PPI

Network-Based Approach

Modular Meta-Analysis

Disease oriented weighting schemes



Weight Scheme

→ weigh each interacting pair of proteins based on gene expression information

→ a discriminative score (DS) that captures the significant expression changes during the transition from **healthy** to **disease** state

DS Calculation

→ nodes and

→ Z-transformed expression values

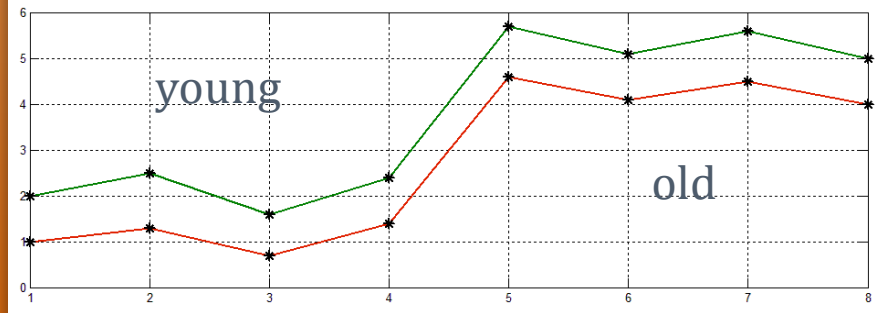
→ activity score

→ discretized activity

→ Condition: class vector (1 for young, 2 for old)

$$DS_{ij} = 1 - NMI(a'_{ij}, condition)$$

Edge weight example



i = [1 1.3 0.7 1.4 4.6 4.1 4.5 4]

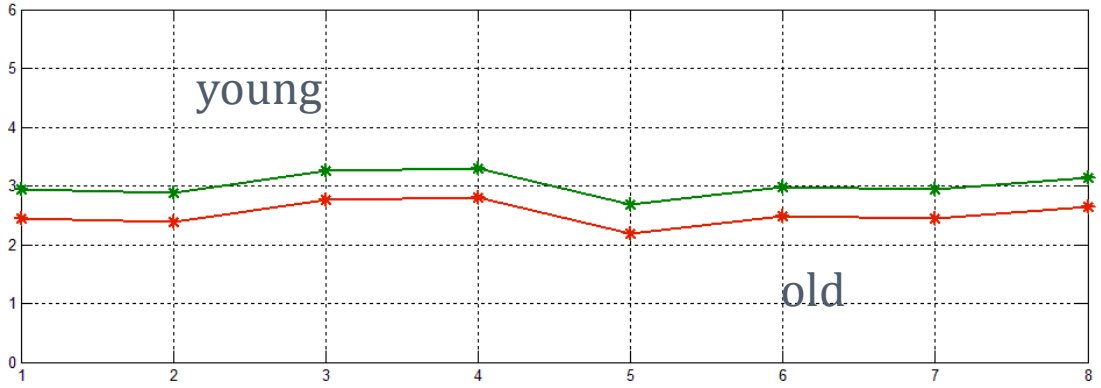
j = [2 2.5 1.6 2.4 5.7 5.1 5.6 5]

$condition$ = [1 1 1 1 2 2 2 2]

a_{ij} = [-1.39 -1.06 -1.67 -1.06 1.56 1.11 1.48 1.03]

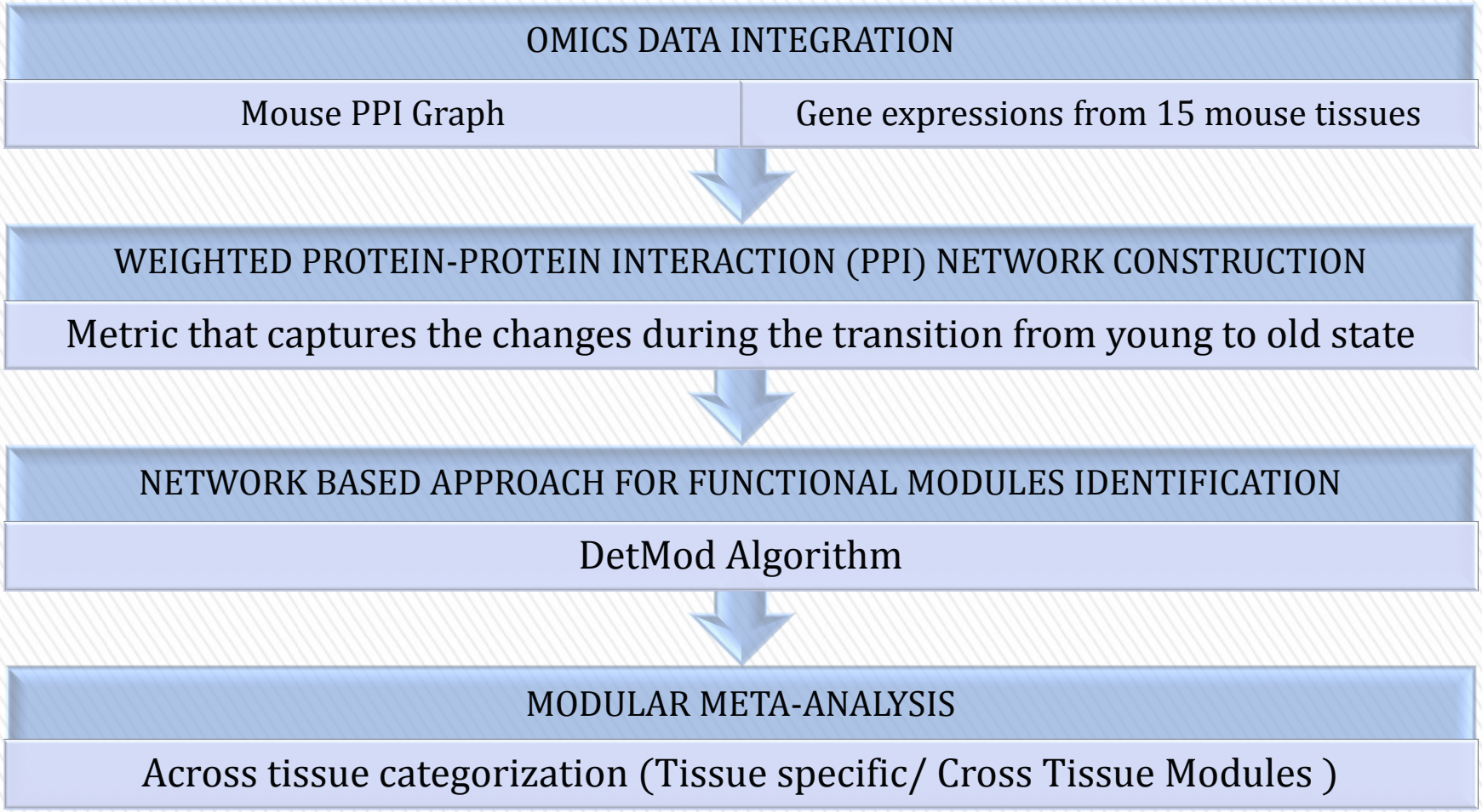
a'_{ij} = [-0.70 -0.70 -2.12 -0.70 2.12 0.70 2.12 0.70]

$$DS_{ij} = 1 - NMI(a'_{ij}, condition) = \mathbf{0.3117}$$



$$DS_{ij} = \mathbf{0.6364}$$

Application: Network-based modular markers of aging across different tissues



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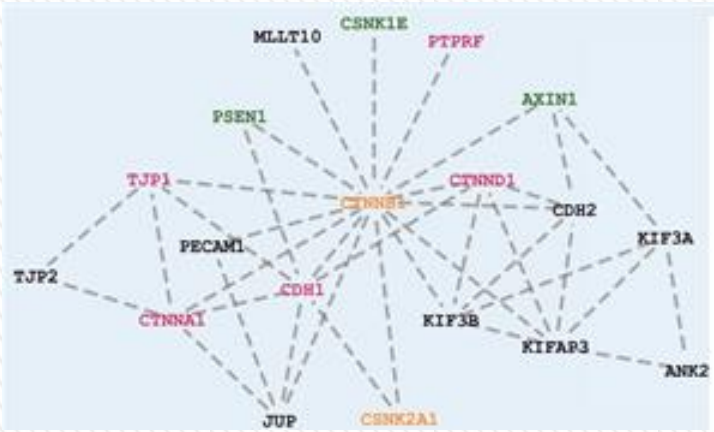
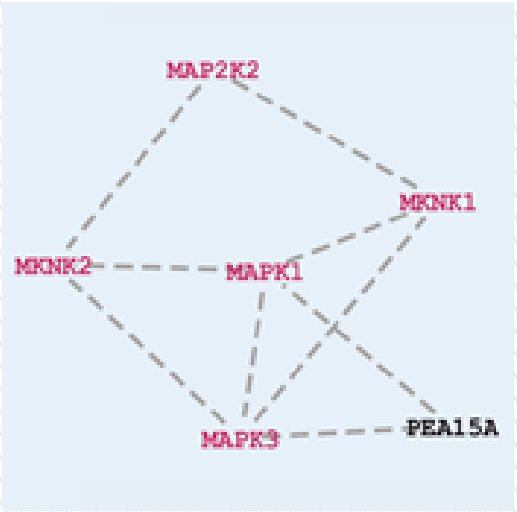
Results





Cross Tissue Module
Is highly enriched (P ≤ E-7) in the adherens junction (pink nodes) and Wnt signaling pathways (green nodes)

Tissue Specific Module (Hippocampus)
is highly enriched in **Insulin signaling/ MAPK signaling pathway**

Vrahatis, A. G., Dimitrakopoulou, K., Dimitrakopoulos, G. N., Sgarbas, K. N., Tsakalidis, A. K., & Bezerianos, A. (2014, January). Network-Based Modular Markers of Aging across Different Tissues. In XIII Mediterranean Conference on Medical and Biological Engineering and Computing 2013 (pp. 1849-1852). Springer International Publishing.

I. Basic Concepts
II. Introduction to Biology
III. Introduction to Biology Networks
IV. Gene Regulatory Networks
V. Protein-Protein Interactions Network
VI. Cell Signaling Networks (Pathway)

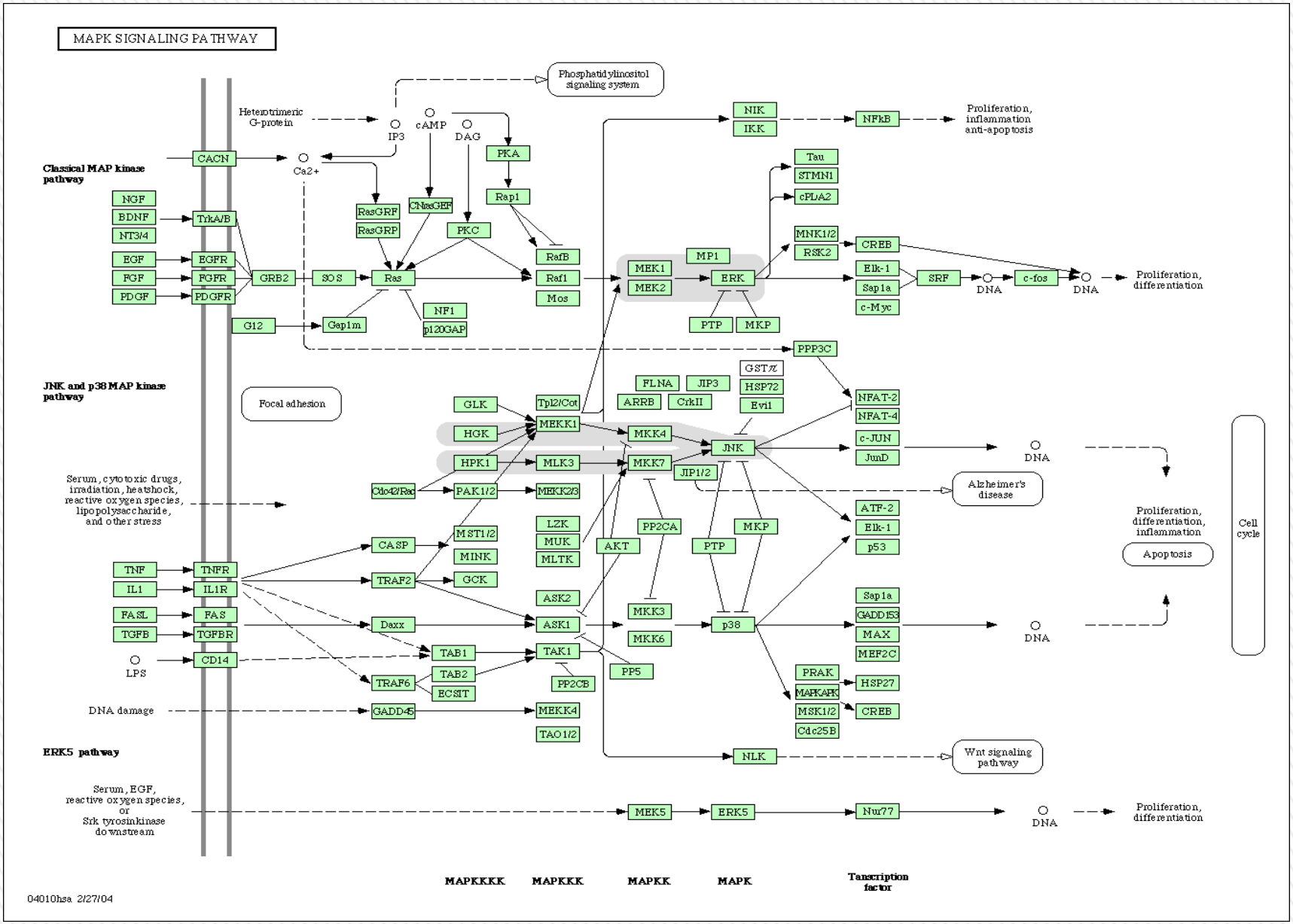
Cell Signaling Networks (Pathways)

- Ordered sequences of signal transduction reactions in a cell
  - Cascade of reversible chemical modifications of proteins
  - E.g., phosphorylation catalyzed by protein kinases

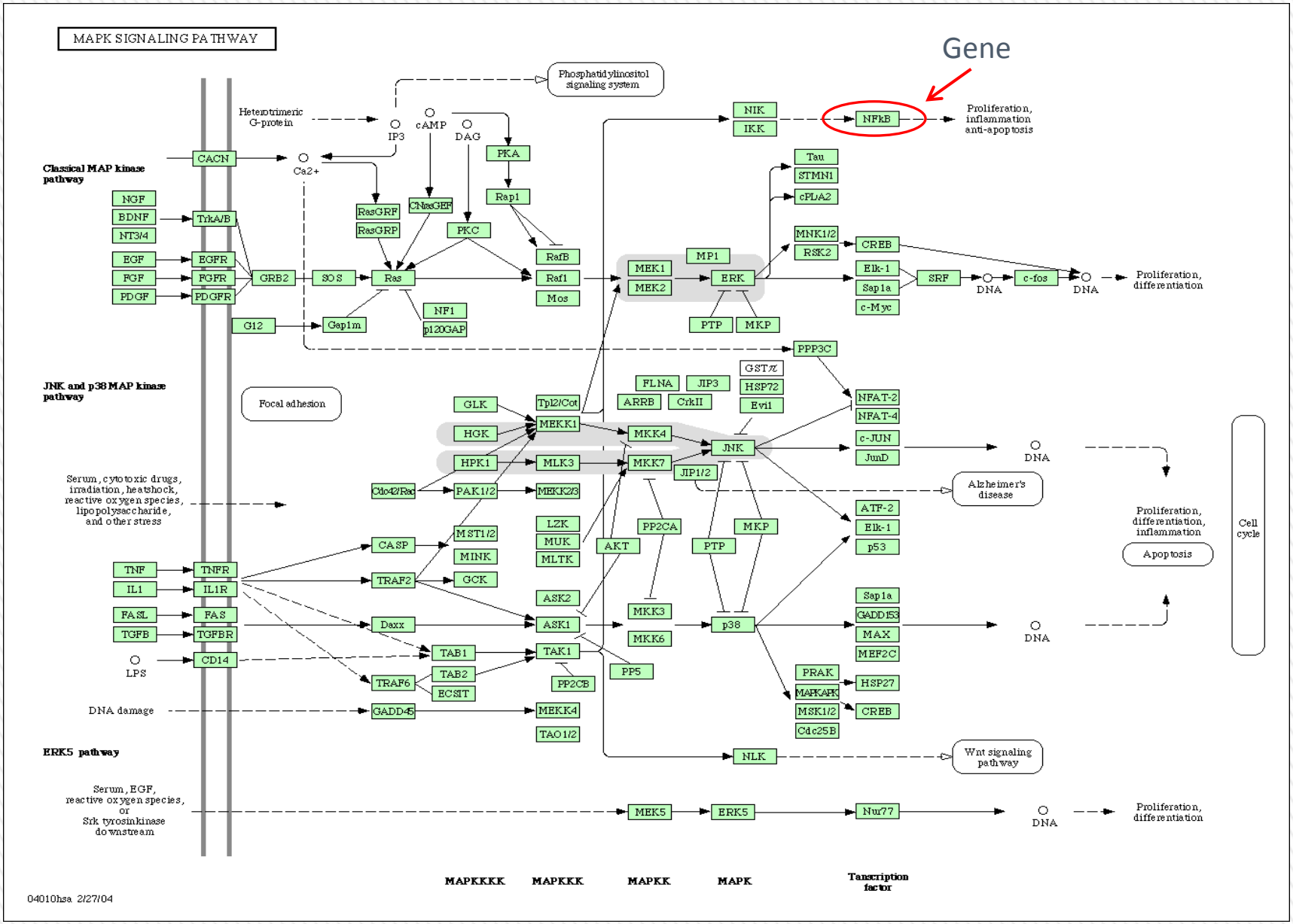
- Signaling pathways in the cell form the *cell signaling network*
  - Nodes are proteins and edges are directed

- Signaling Pathway Networks
  - In biology a signal or biopotential is an electric quantity (voltage or current or field strength), caused by chemical reactions of charged ions. refer to any process by which a cell converts one kind of signal or stimulus into another.
  - Another use of the term lies in describing the transfer of information between and within cells, as in signal transduction.

A Pathway Example



A Pathway Example



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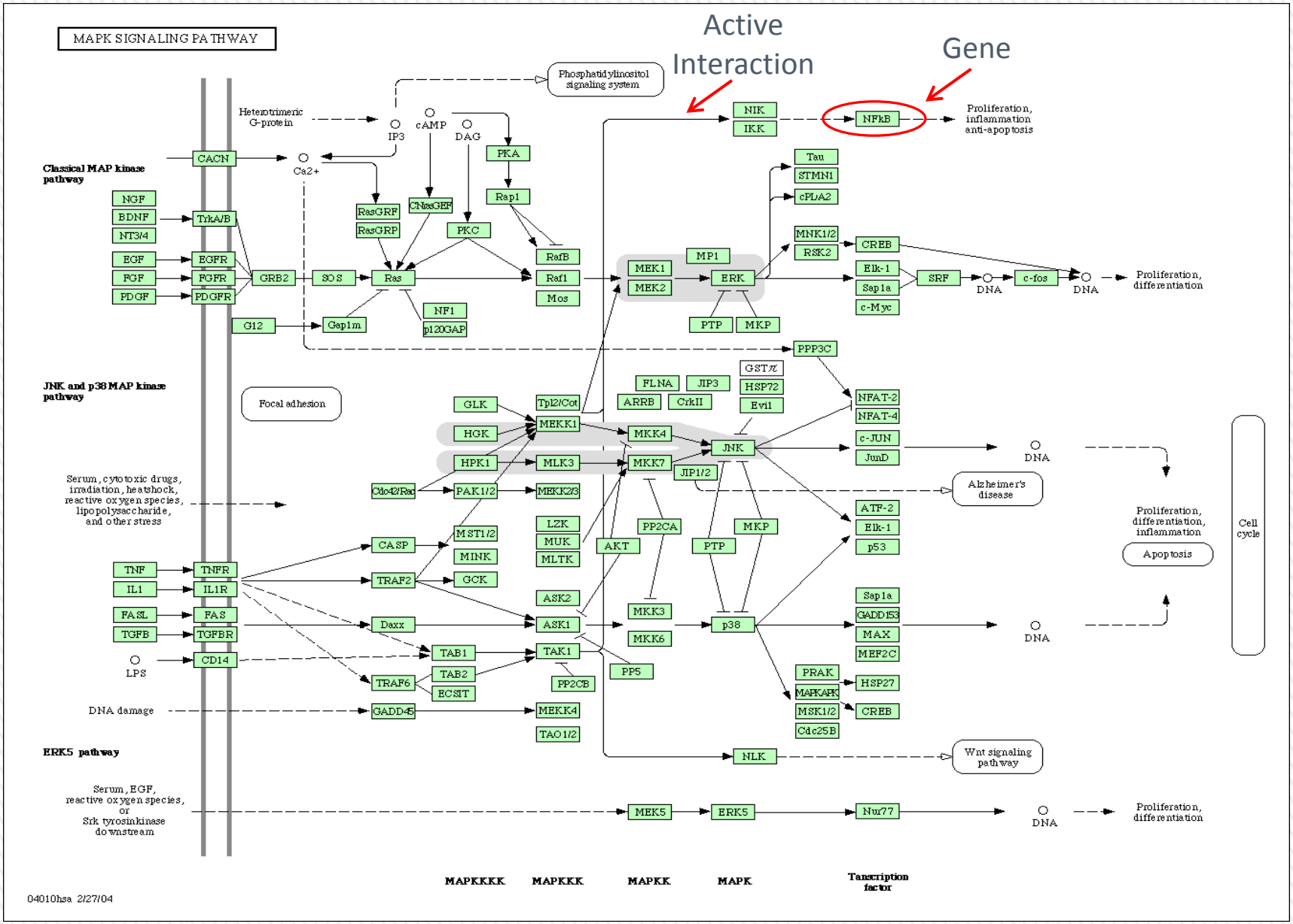
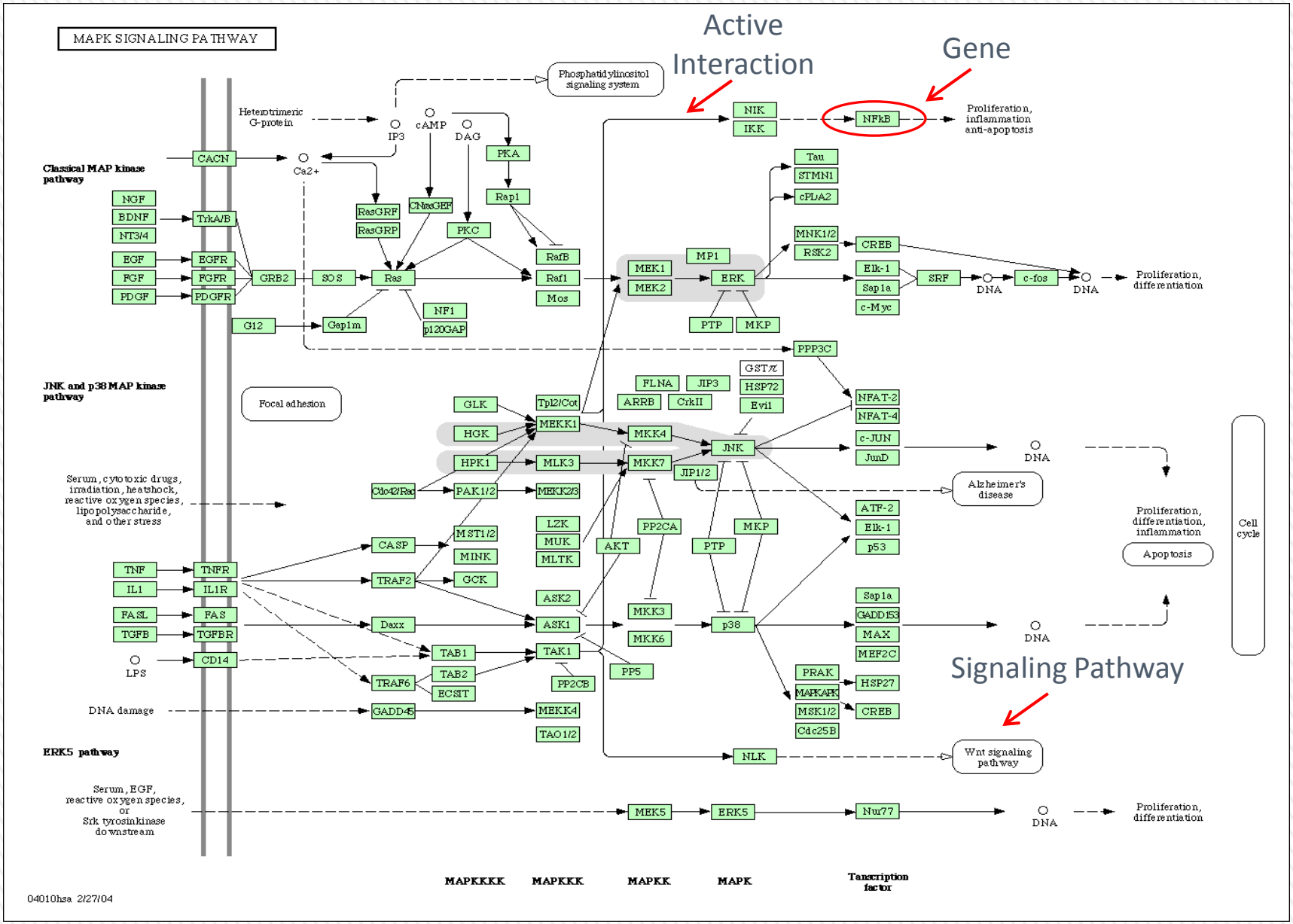
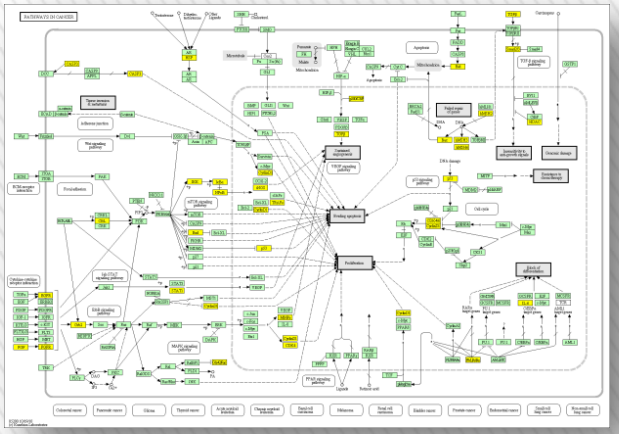


A Pathway Example

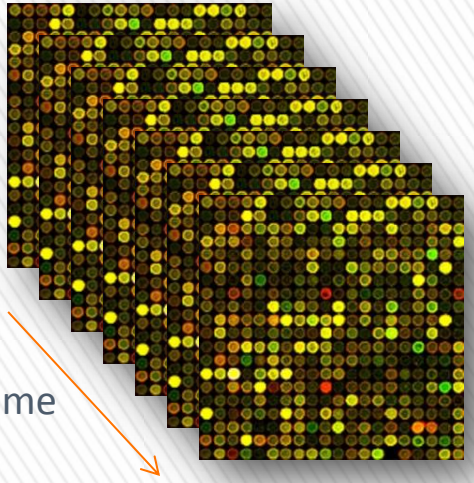


Ongoing project: Time-Varying Integromics Approach in Pathways

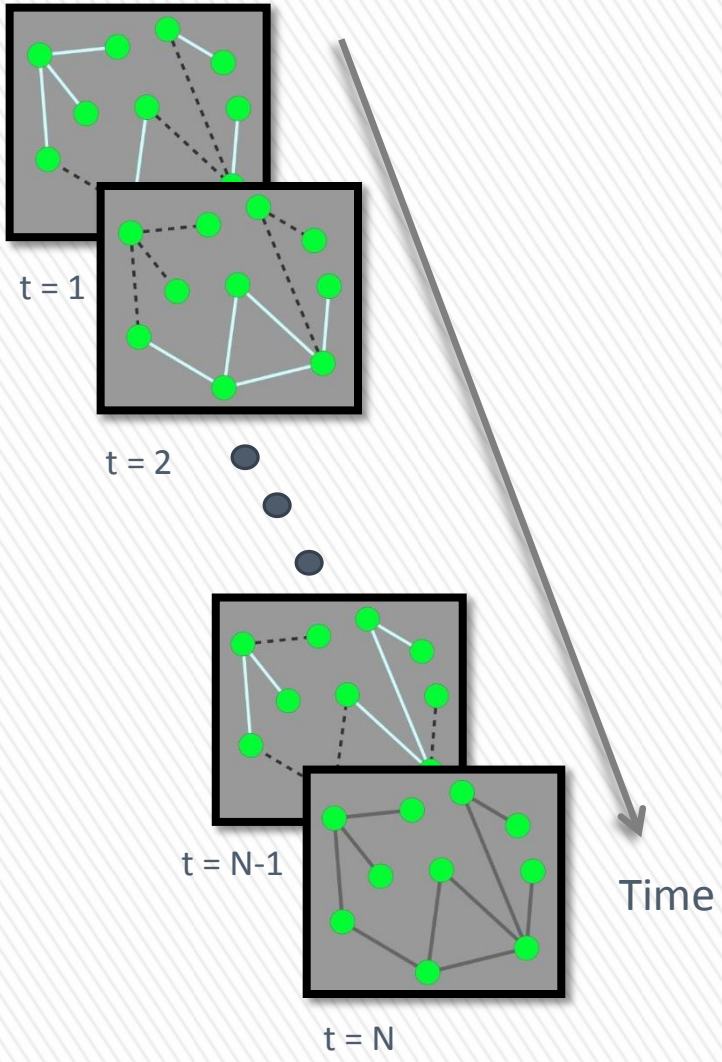
Pathway Map



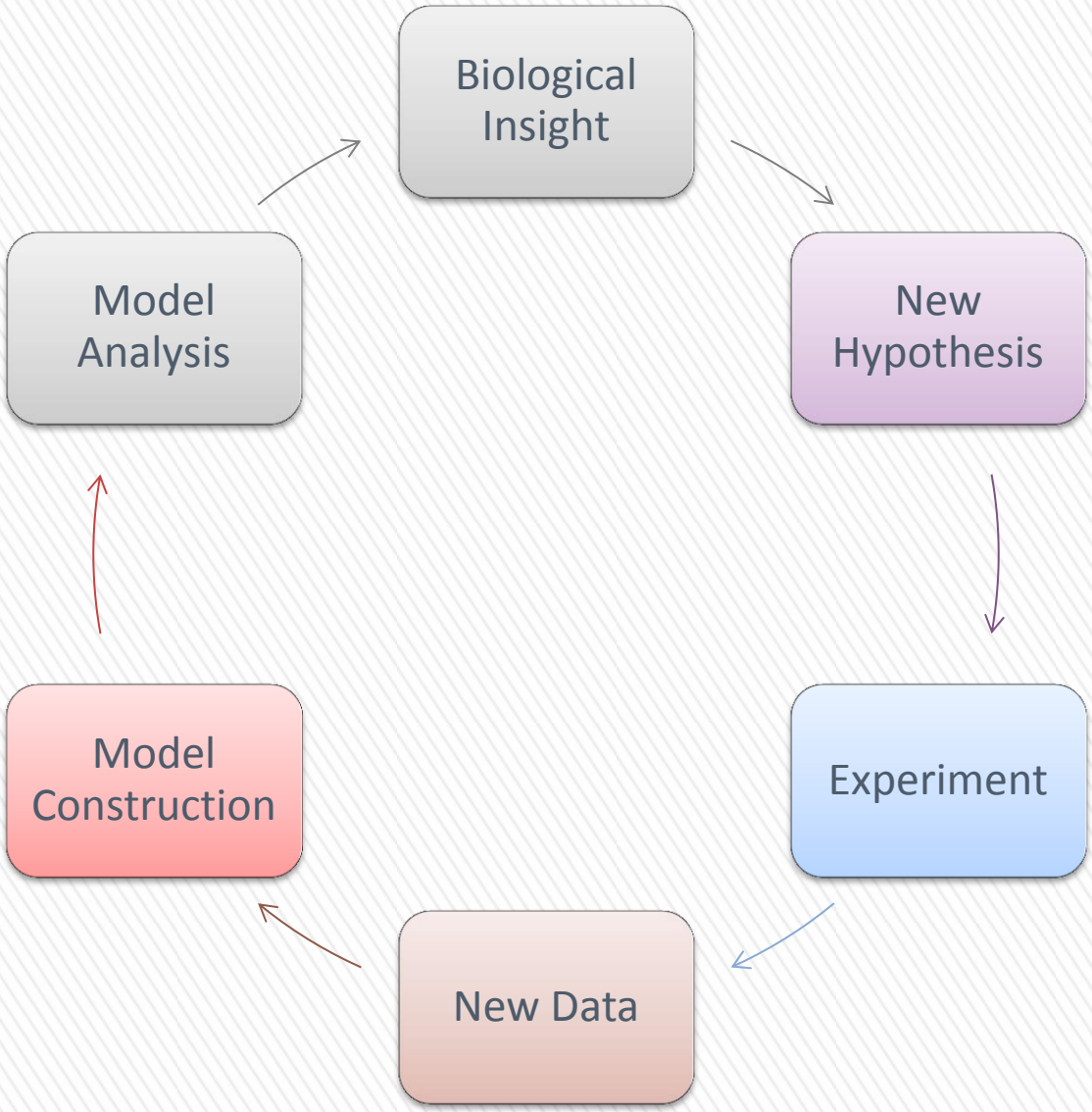
Gene expressions



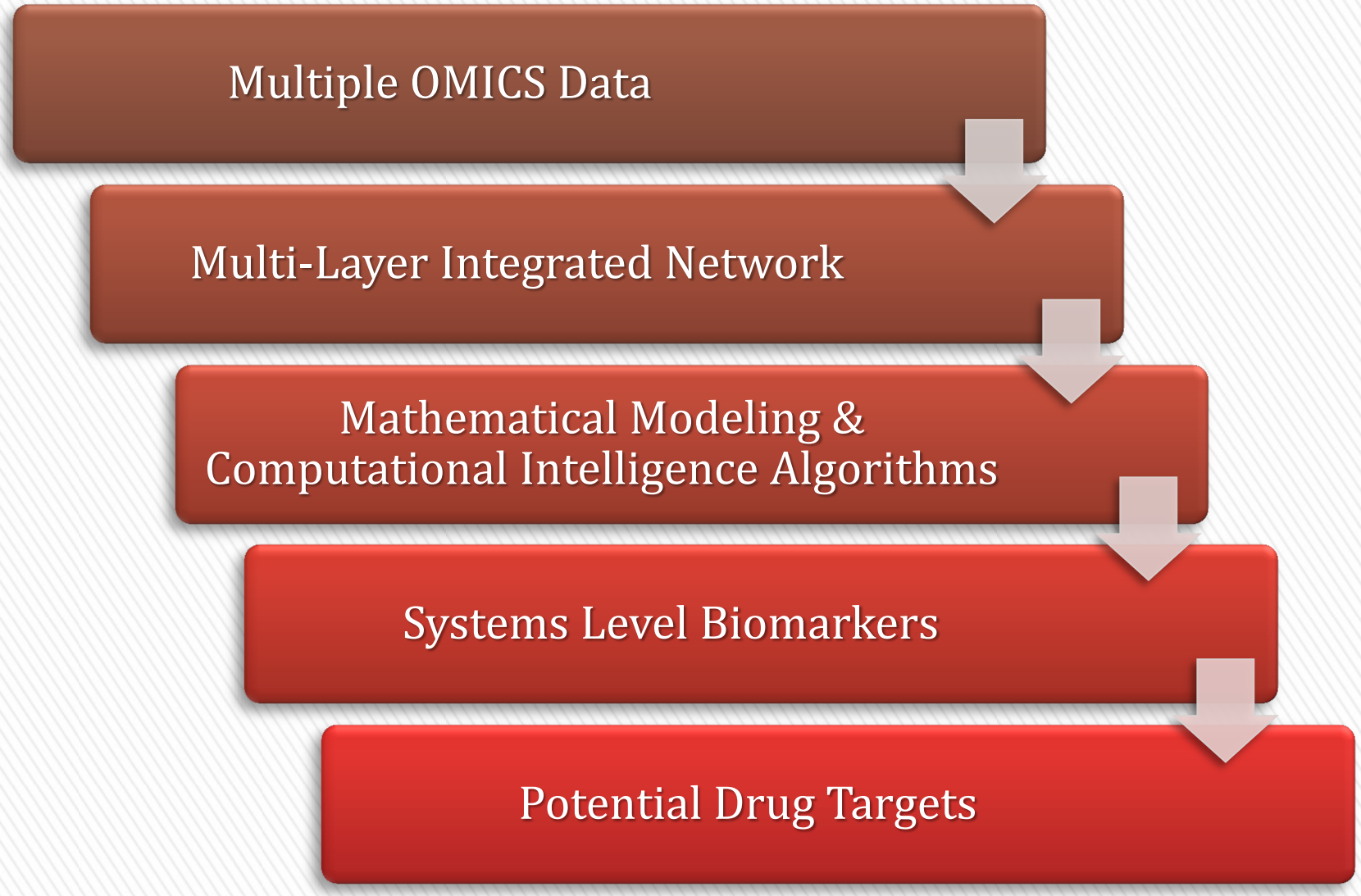
Time Varying Network



Systems Biology at a glance

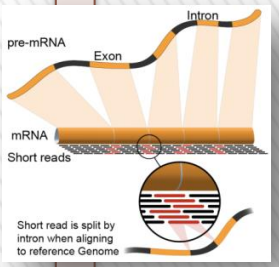


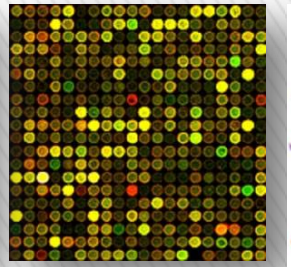
SYSTEMS MEDICINE IN THE INTEGROMICS ERA

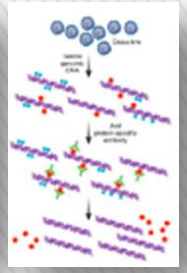


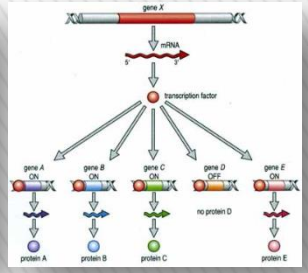
Our Laboratory

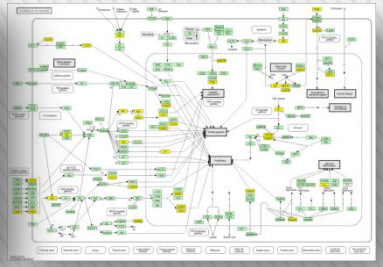
Multiple OMICS Data





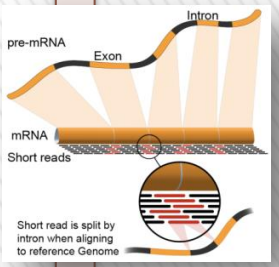


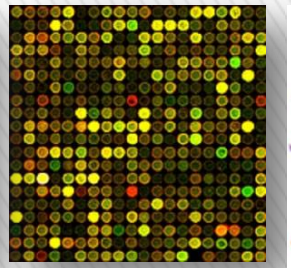


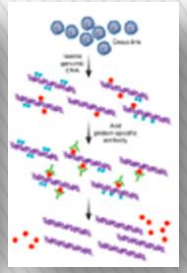


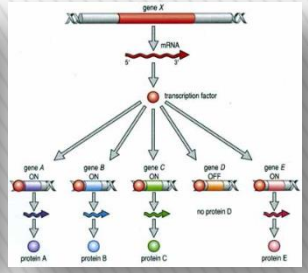
Our Laboratory

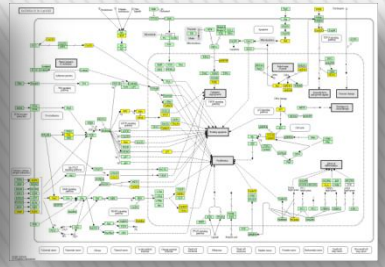
Multiple OMICS Data



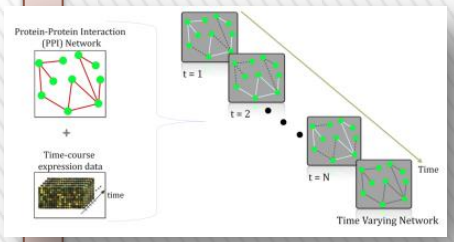


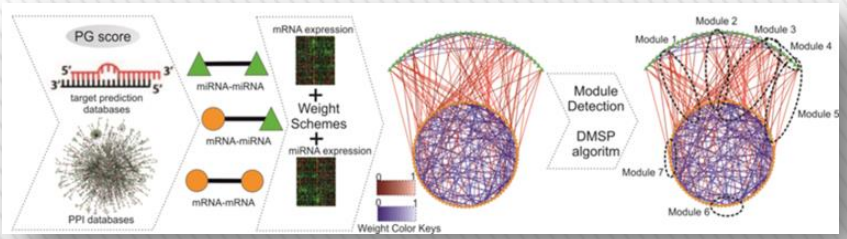


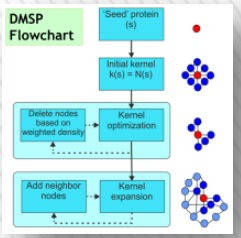


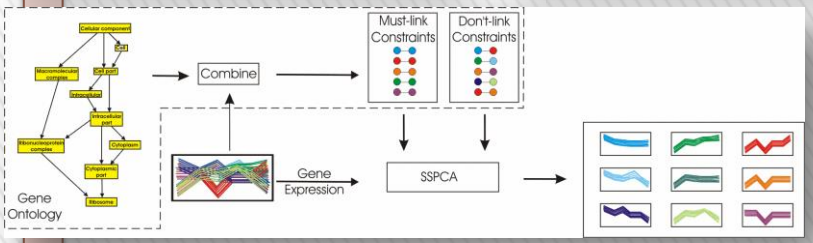


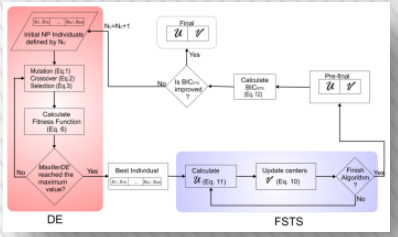
Mathematical Modeling & Computational Intelligence Algorithms

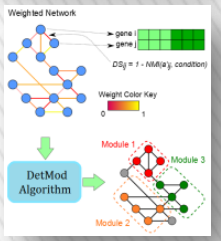






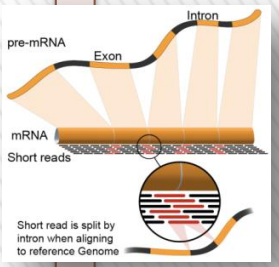


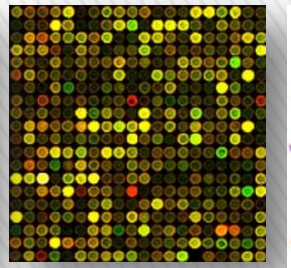


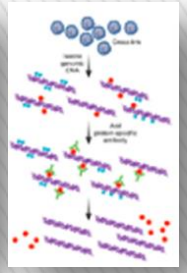


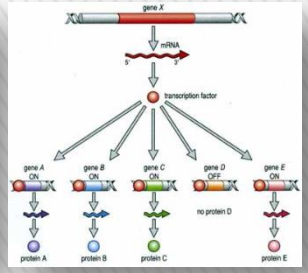
Our Laboratory

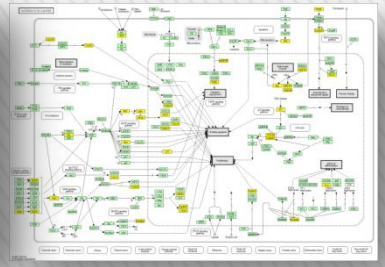
Multiple OMICS Data



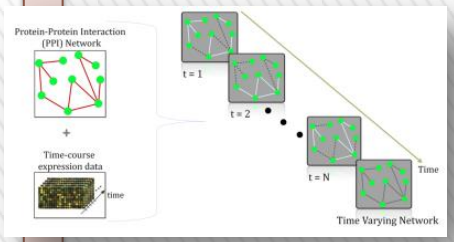


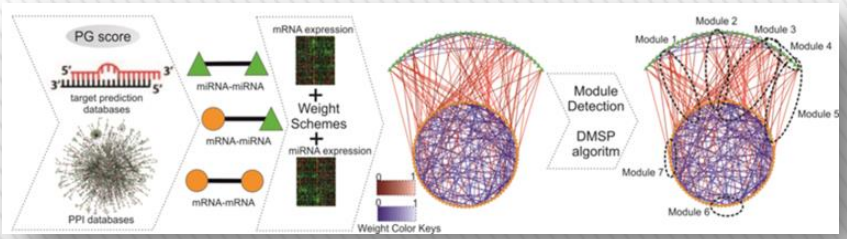


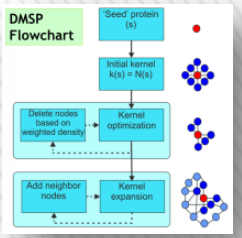


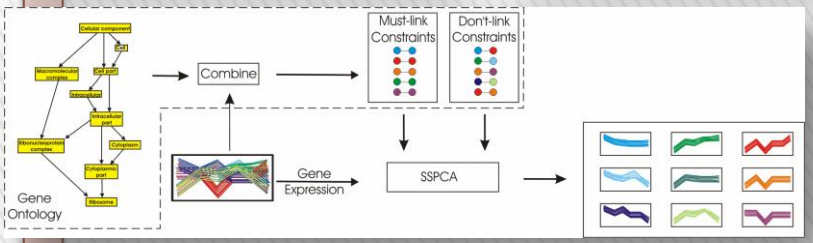


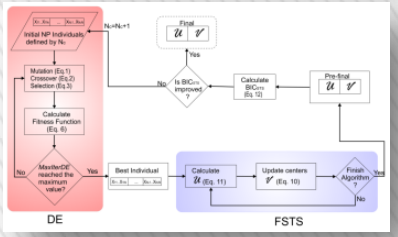
Mathematical Modeling & Computational Intelligence Algorithms

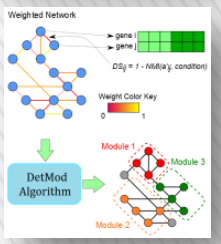








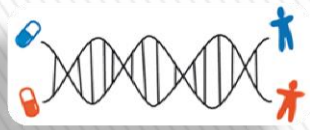




Systems Medicine Biomarkers

Personalized Medicine

Personalized Drug Development



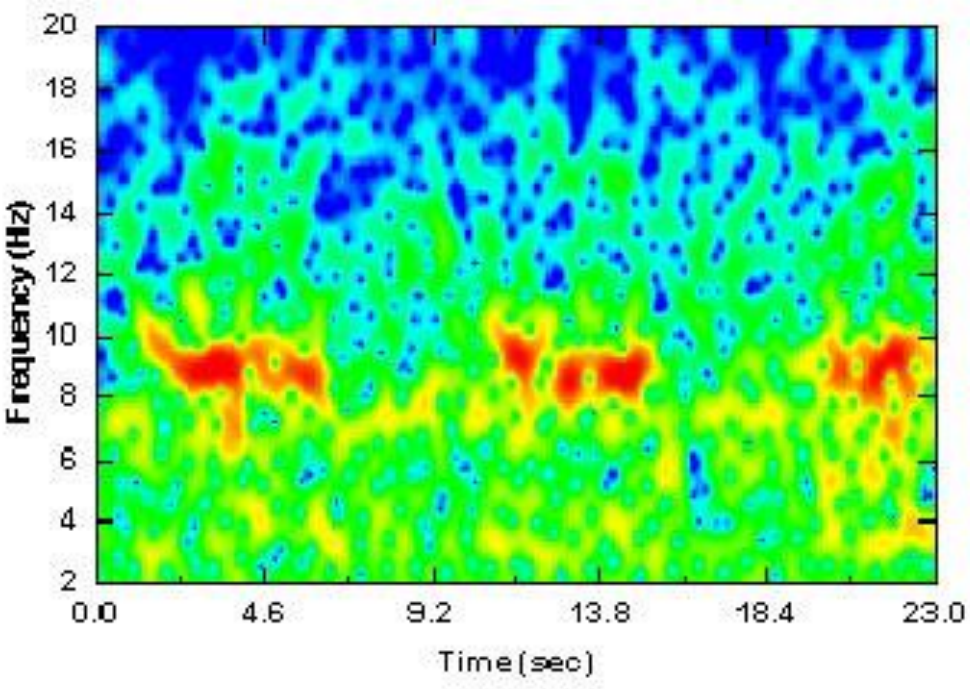
Part 2:
Complexity of Brain Networks

Part 2:
Dynamic Brain Connectivity Mapping

Introduction to Electroencephalography (EEG)

Electroencephalography (EEG)

- EEG Records the current flow in cortical areas, tracking tiny electrical impulses that caused by brain cells communication.



Characteristics

- The EEG is typically described in terms of rhythmic activity. The rhythmic activity is divided into bands by frequency: Delta, Theta, Alpha, Beta and Gamma.

	Frequency	Location	
Delta	< 4Hz	Frontally in adults, posteriorly in children; high amplitude waves	Adults slow wave sleep; Babies
Theta	4 – 7Hz	Found in locations not related to task at hand	Young children; Drowsiness or arousal in older childen and adults; idling
Alpha	8 – 12Hz	posterior regions of head, both sides, higher in amplitude on dominant side. Central sites (c3-c4) at rest .	Relaxed/reflecting; Closing the eyes
Beta	12 – 30 Hz	both sides, symmetrical distribution, most evident frontally; low amplitude waves	Alert/Working; Active busy or anxious thinking, active concertration
Gamma	> 30Hz	Somatosensory cortex	Short term memory matching of recognized objects, sounds or tactile sensations; Cross-modal sensory processing

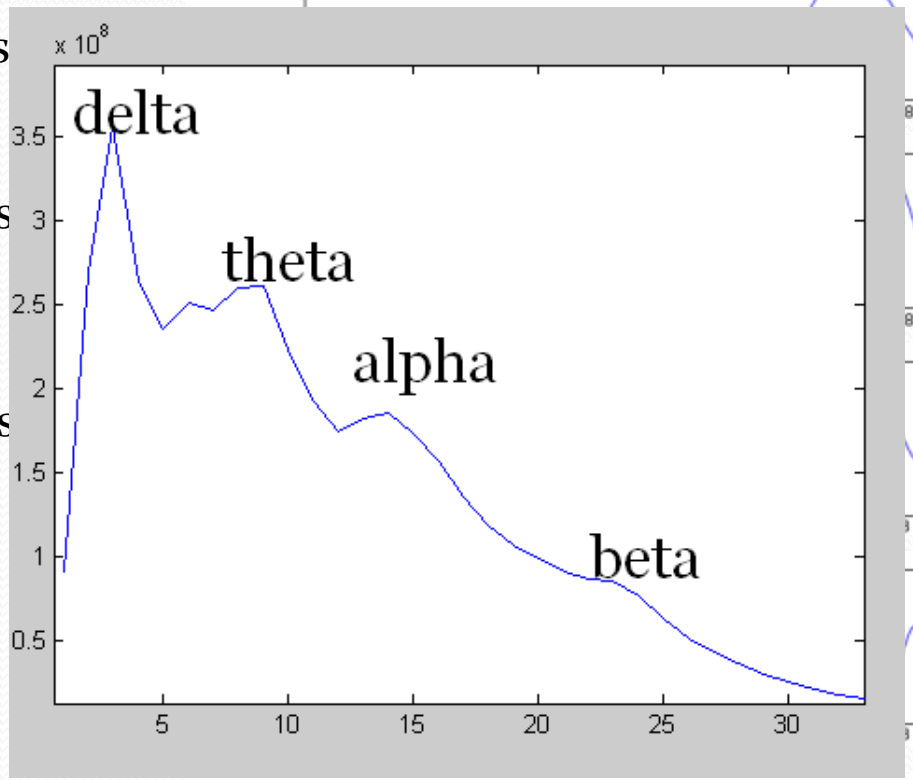
EEG rhythmic activity

Delta waves

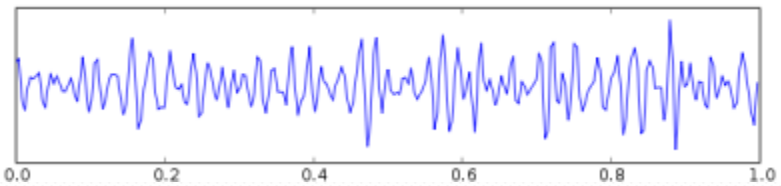
Theta waves

Alpha waves

Beta waves

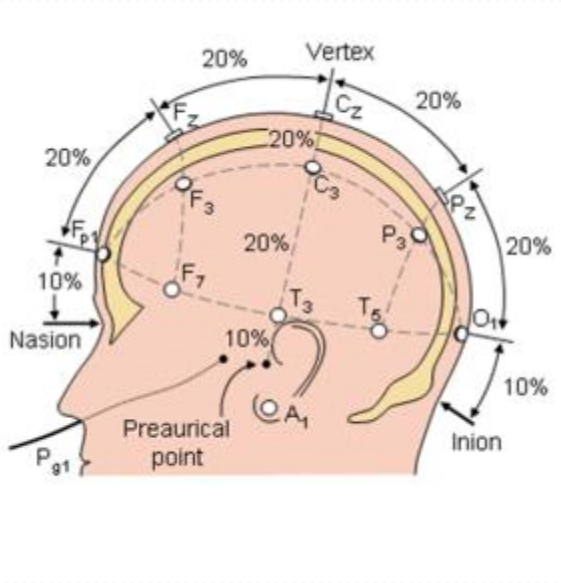


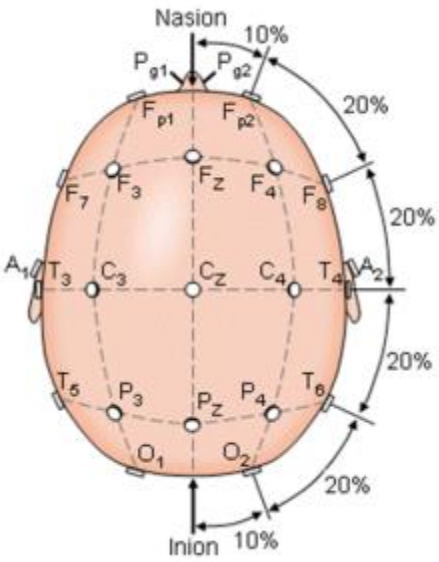
Gamma waves > 30Hz

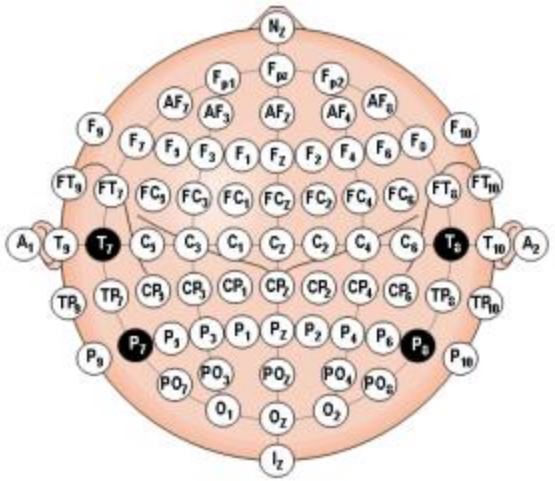


EEG Recording

- The faint electrical activity is measured by putting electrodes on the scalp. Small metal discs with thin wires (electrodes) are placed on the scalp, and then send signals to a computer to record the results.







EEG Recording

An **EEG recording net** (Electrical Geodesics, Inc.) being used on a participant in a brain wave study.

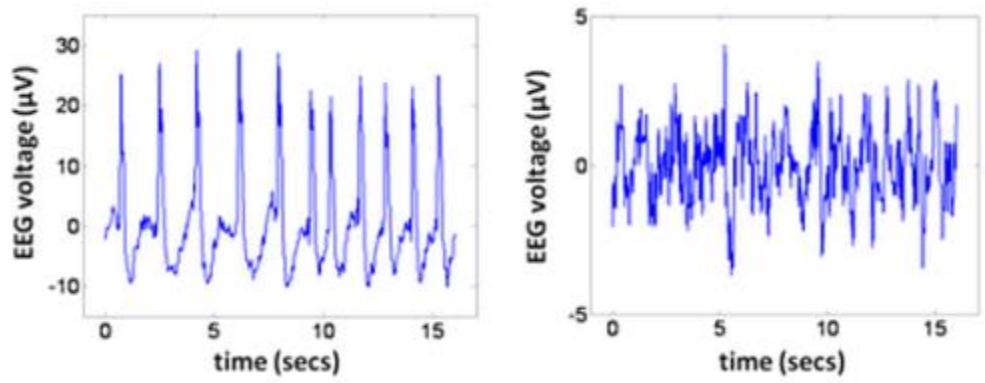
EEG Electrodes

The Neuroscan SynAmps2 amplifier, power supply, and 70-channel headbox (left)

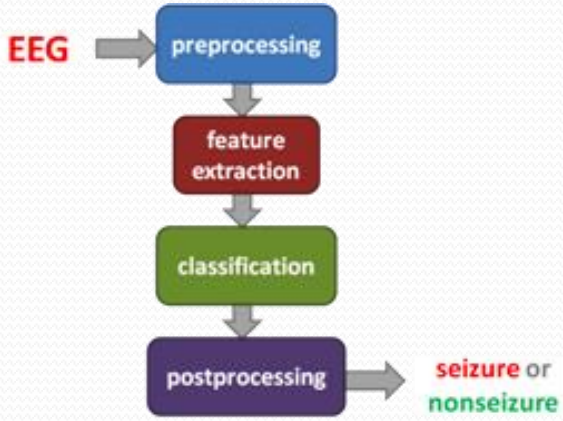
Objectives of EEG study

- The EEG is used in the evaluation of brain disorders. Most commonly it is used to show the type and location of the activity in the brain during a seizure.
- It also is used to evaluate people who are having problems associated with brain function. These problems might include confusion, coma, tumors, long-term difficulties with thinking or memory, or weakening of specific parts of the body (such as weakness associated with a stroke).
- An EEG is also used to determine brain death. It may be used to prove that someone on life-support equipment has no chance of recovery.

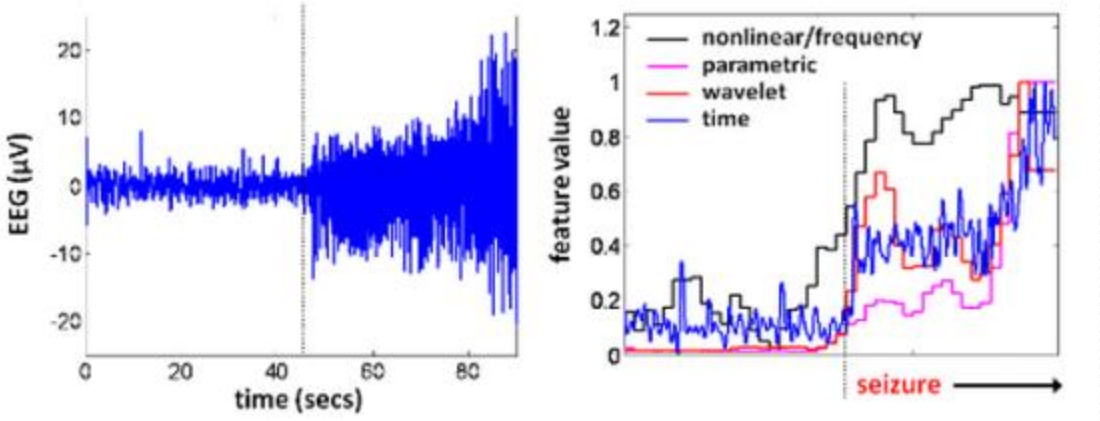
Example of Seizure detection study

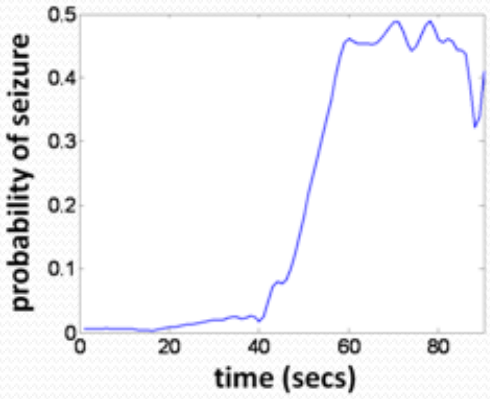


Newborn EEG seizure and nonseizure patterns



EEG processing for seizure detection





Neonatal Brain Research Group, University College Cork, Wilton, co. Cork, Ireland

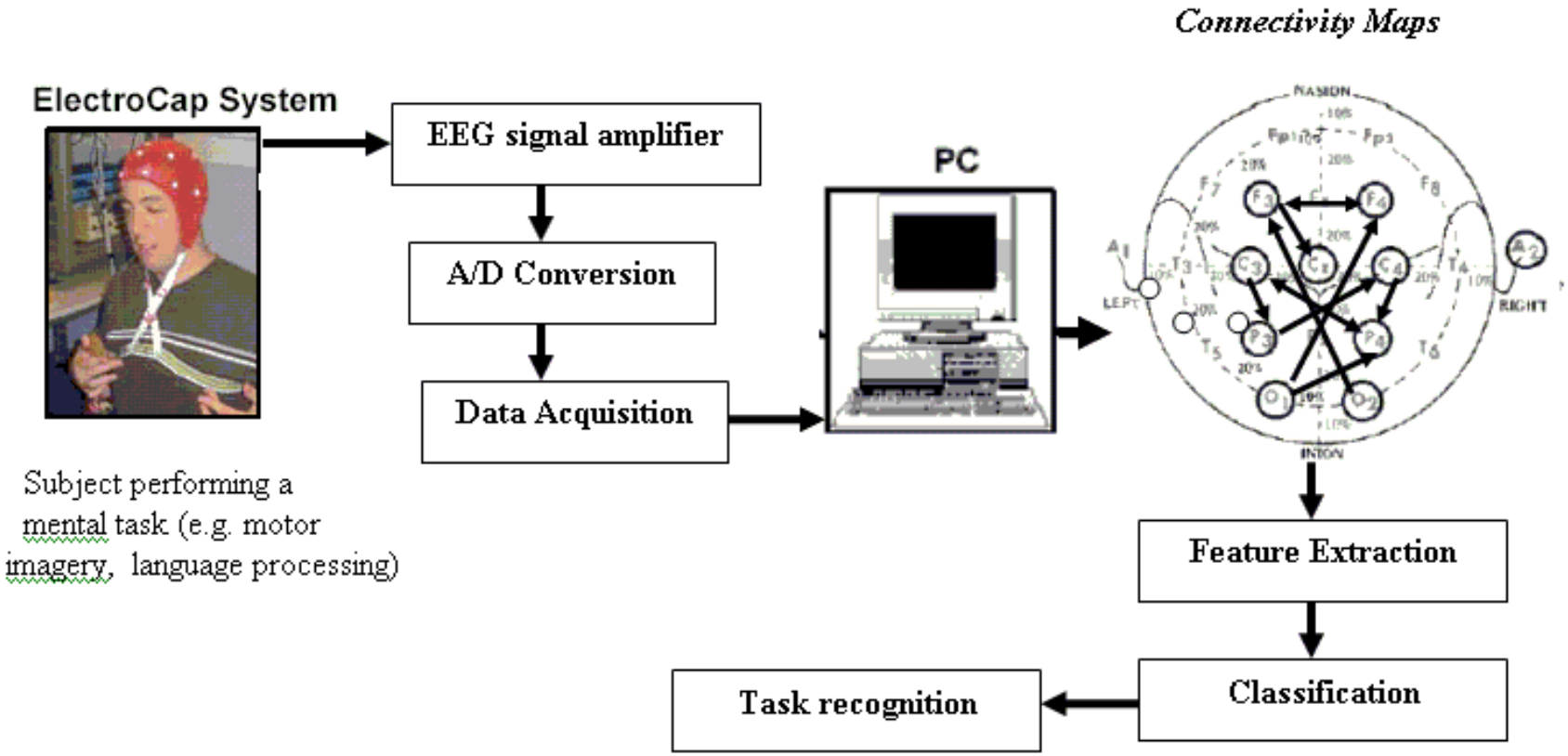
Functionally event results

ERP (Event-related potentials)	ERS (Event-related synchronization)	ERD (Event-related desynchronization)
phase-locked	not phase-locked	not phase-locked
	Closing eyes and relaxation: **increase** in alpha (9-12 Hz)	Hand movement: **decrease** in Mu rhythm (9-13 Hz)

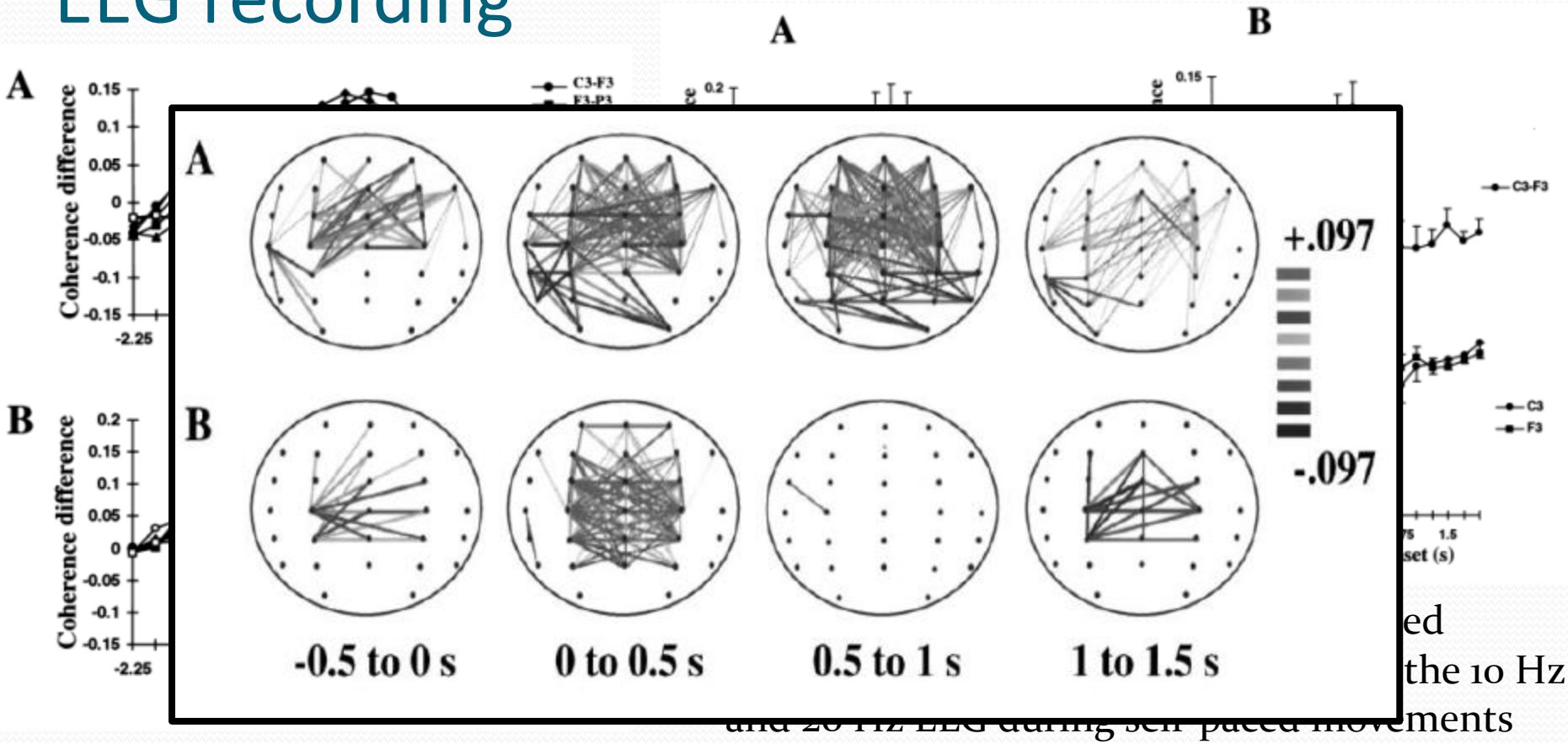
Neural connectivity based on EEG recording

- In EEG recording, each electrode records current from many sources, all electrodes are correlated with each other.
- The estimation of brain connectivity allows describing the functional links established between different cortical areas during the execution of a particular experimental task and is an important step to the understanding of the brain functional organization.

Neural connectivity based on EEG recording



Neural connectivity based on EEG recording



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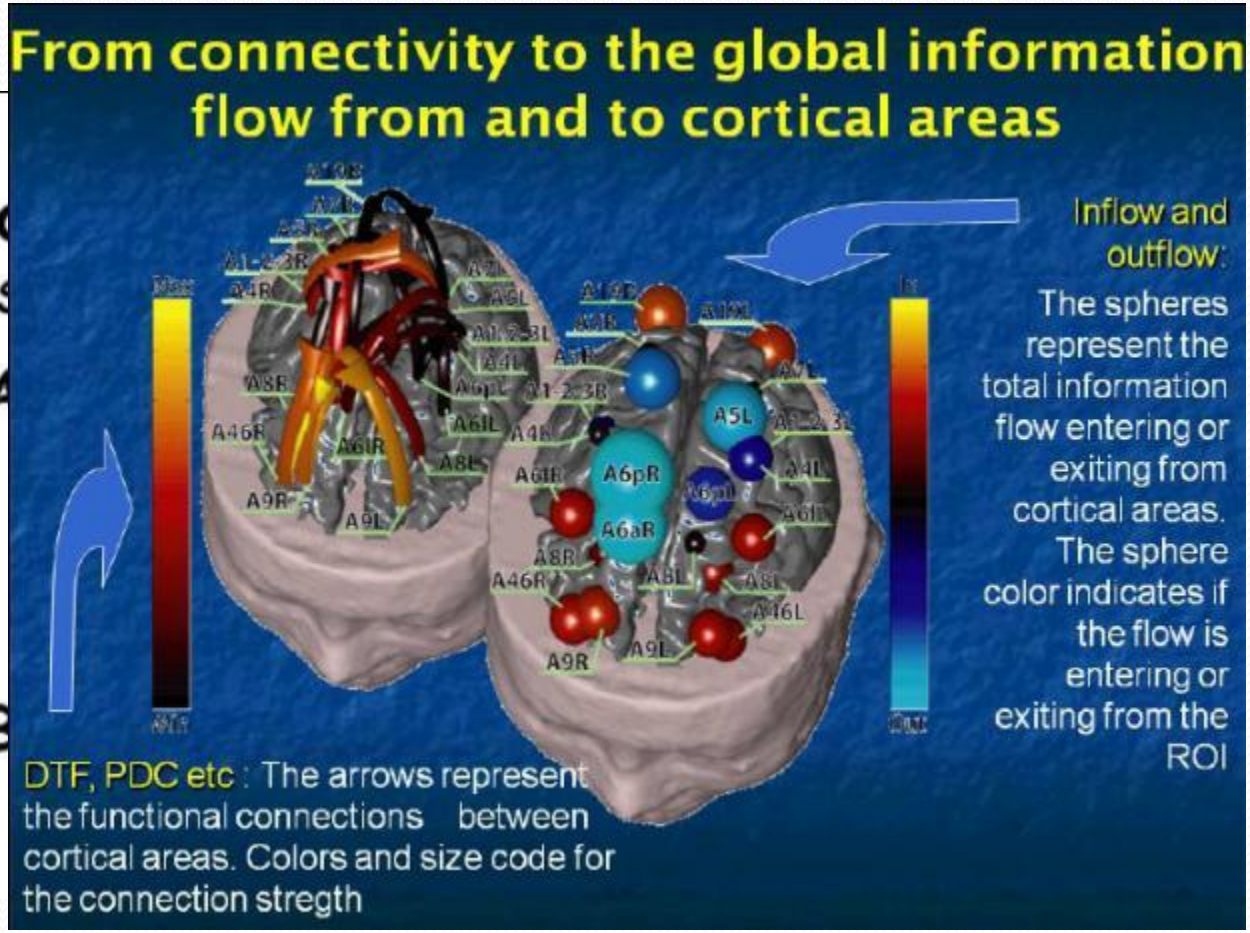
L. Leocani and M. Hallett , "Event-related coherence and event-related desynchronization/synchronization in the 10 Hz and 20 Hz EEG during self-paced movements", Frontiers in Science, 2010

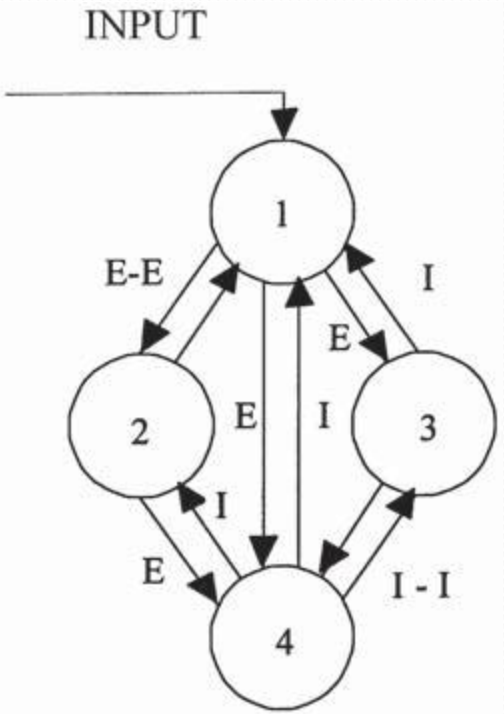
Neural connectivity based on EEG recording



L. Astolfi and F. Babiloni, "Methods for monitoring effects of drugs and other chemicals in the CNS by using high resolution EEG", Frontiers in Science, 2010

Methodology of Brain Connectivity

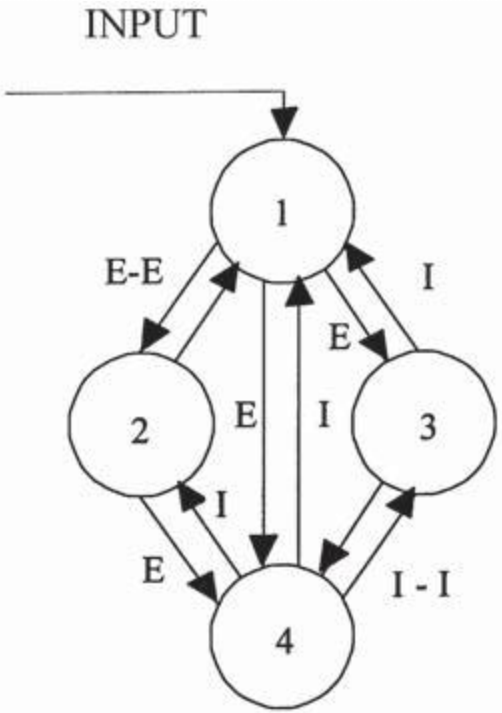
Definitions_1



W.J. Freeman et al. / BioSystems 59 (2001)

- Brain connectivity is viewed as central for the understanding of the organized behavior of cortical regions.
- Aim at describing these interactions as connectivity patterns which hold the direction and strength of the information flow between cortical areas.

Definitions_2



W.J. Freeman et al. / BioSystems 59 (2001)

- Defined as the temporal correlation between spatially remote neurophysiologic events.
- The connection methods typically involve the estimation of some covariance properties between the different time series measured from the different spatial sites, during motor and cognitive tasks based on EEG and ECoG .

Coherence

- Due to the evidence that important information in the brain signals are coded in frequency rather than in time domain, spectral coherence between the activity of pairs of channels is focused to detect frequency-specific interactions in EEG or ECoG signals.
- The coherence between multi-channel series [$x_1(t)$ … $x_N(t)$] is a real-valued function that is defined as:

$$\eta_{kl}(f) = \frac{S_{kl}(f)}{\sqrt{S_{kk}(f)S_{ll}(f)}}$$

where $S_{kl}(f)$ is an element of spectral matrix $S(f)$, and spectral matrix is defined by multivariate model:

Coherence

- multivariate model is defined as:

$$X(t) = -\sum_{\tau=1}^{p} A_\tau X(t-\tau) + E(t)$$

where $X(t)= [x_1(t) \ldots x_N(t)]$, N represents channels number, and p is the model order.

- When we use Fourier transform to both side:

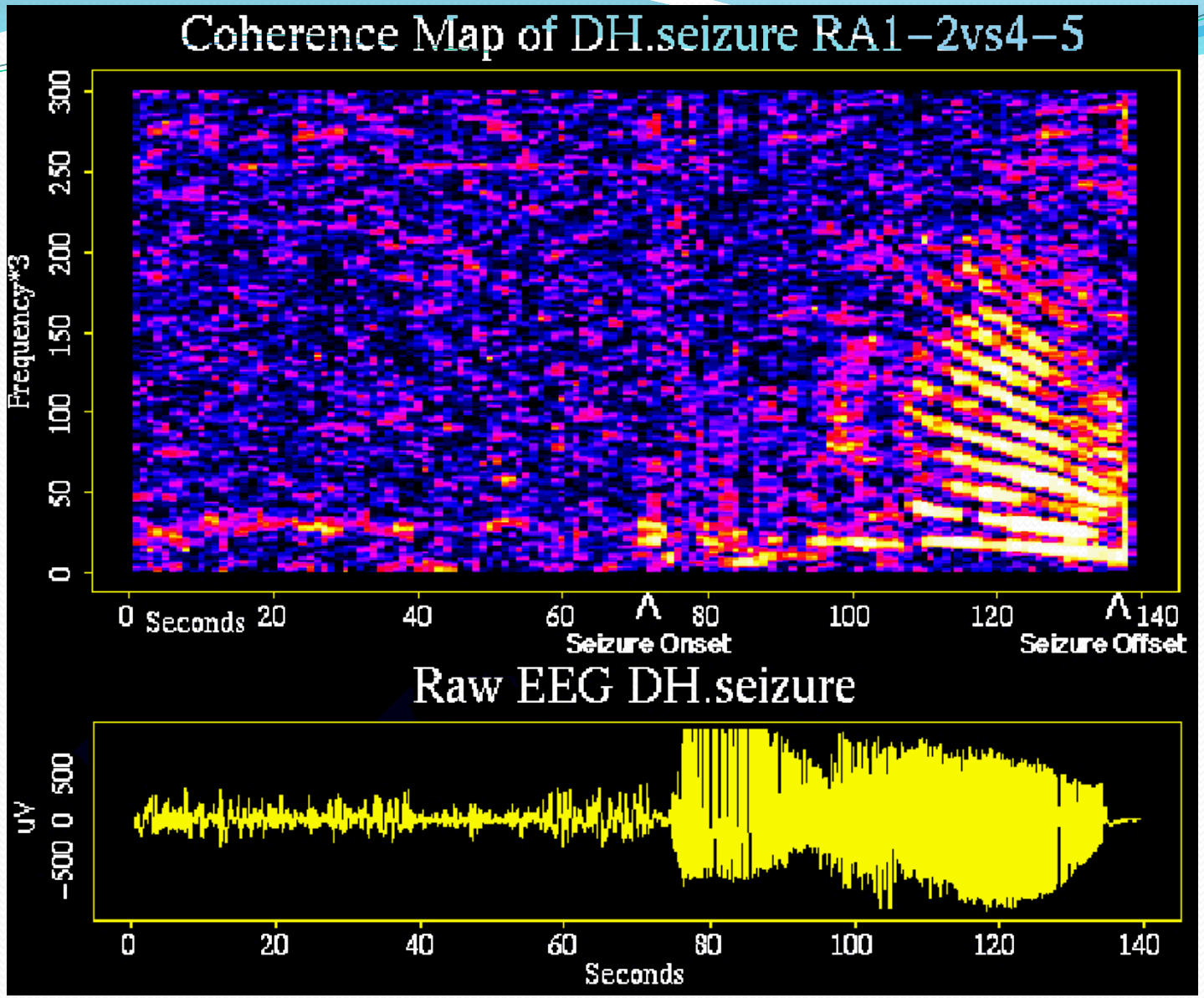
$$X(f) = H(f)E(f)$$

where $H(f)$ is the transfer function: $H(f) = \left(\sum_{\tau=0}^{p} A_\tau e^{-i2\pi f \Delta t} \right)^{-1}$

- By these, we obtain spectral matrix

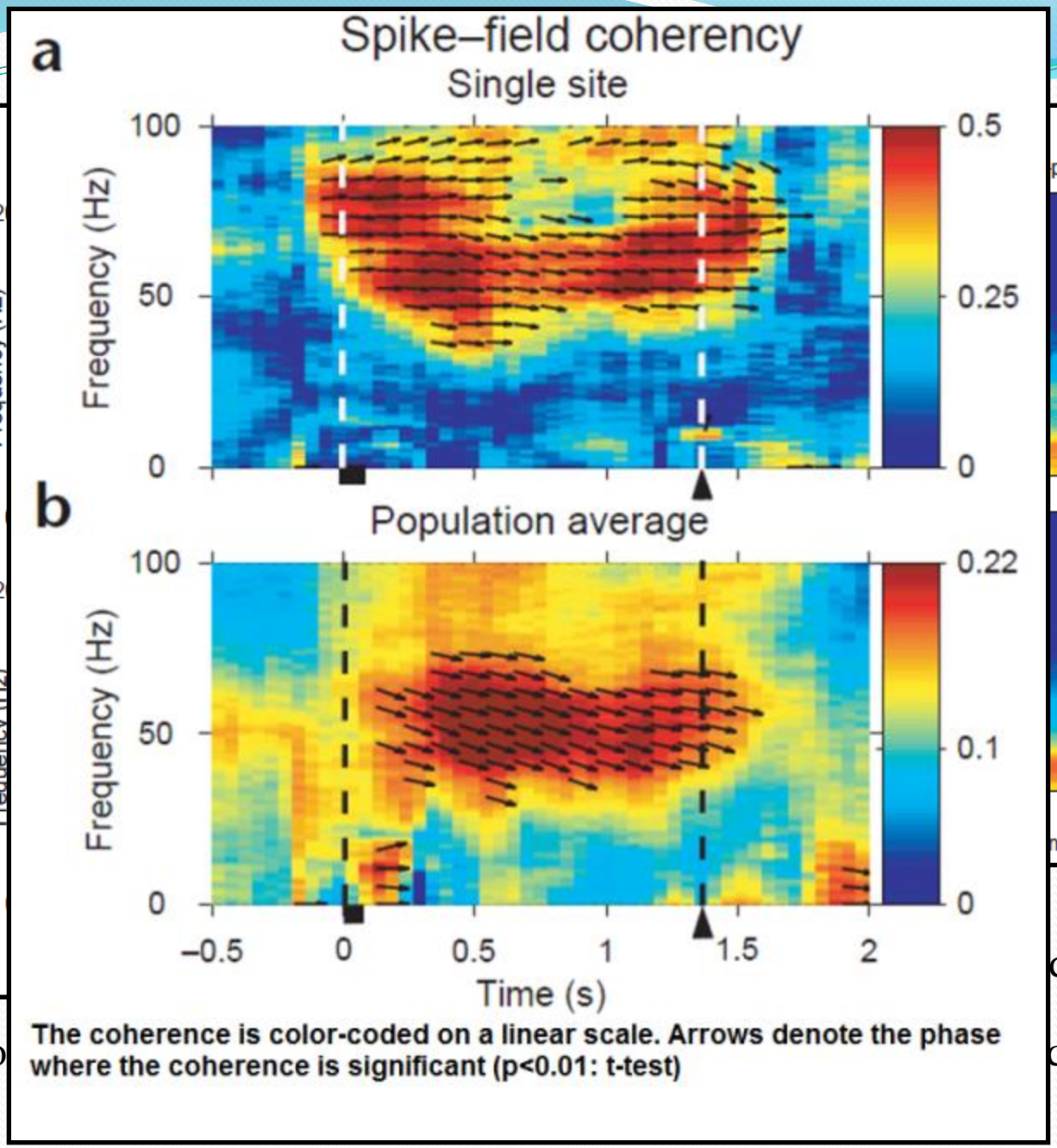
$$S(f) = H(f) \sum H^{*}(f)$$

where $\sum$ is the noise covariance matrix.



Coherence Analysis of Human Depth EEG During Seizure Activity

John Klopp et.al., 1996, Complexity International



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Bijan Pesaran et al., 2002, Nature Neuroscience

Partial Coherence

- In order to distinguish between direct and cascade flows, partial coherence was proposed. It could be defined in terms of MVAR coefficients transformed to the frequency domain.
- The formal definition of the normalized Partial Directed Coherence (PDC) is the following:

$$\chi_{lk}^{2}(f) = \frac{M_{lk}^{2}(f)}{M_{ll}(f) M_{kk}(f)}$$

where $M_{ll}(f)$ is an element of the inverse of spectral matrix $S(f)$. Partial coherence describes direct relationships between signals

Directed connection

- However, coherence analysis has not a directional nature, actually, it just examines whether a link exists between time series, by describing instances when they are in synchronous activity, and it does not provide the direction of the information flow.
- Multivariate spectral techniques called Directed Transfer Function (DTF) or Partial Directed Coherence (PDC) were proposed to determine the directional influences between any given pair of channels in a multivariate data set. Both DTF and PDC can be demonstrated to rely on the key concept of Granger causality between time series(Granger, C., 1969).

Granger Causality

- Granger theory mathematically defines what a “causal” relation between two signals is. According to this theory, an observed time series x(n) is said to cause another series y(n) if the knowledge of x(n)’s past significantly improves prediction of y(n); this relation between time series is not necessarily reciprocal, i.e., x(n) may cause y(n) without y(n) causing x(n). This lack of reciprocity allows the evaluation of the direction of information flow between structures.

Granger Causality

- The Granger causality at frequency *f* is obtained as the fraction of the total power at that frequency at one electrode that can be explained by the causal influence from the other electrode. The value ranges from 0 to 1, where 0 represents no causal influence and 1 denotes total causal influence from the other electrode.

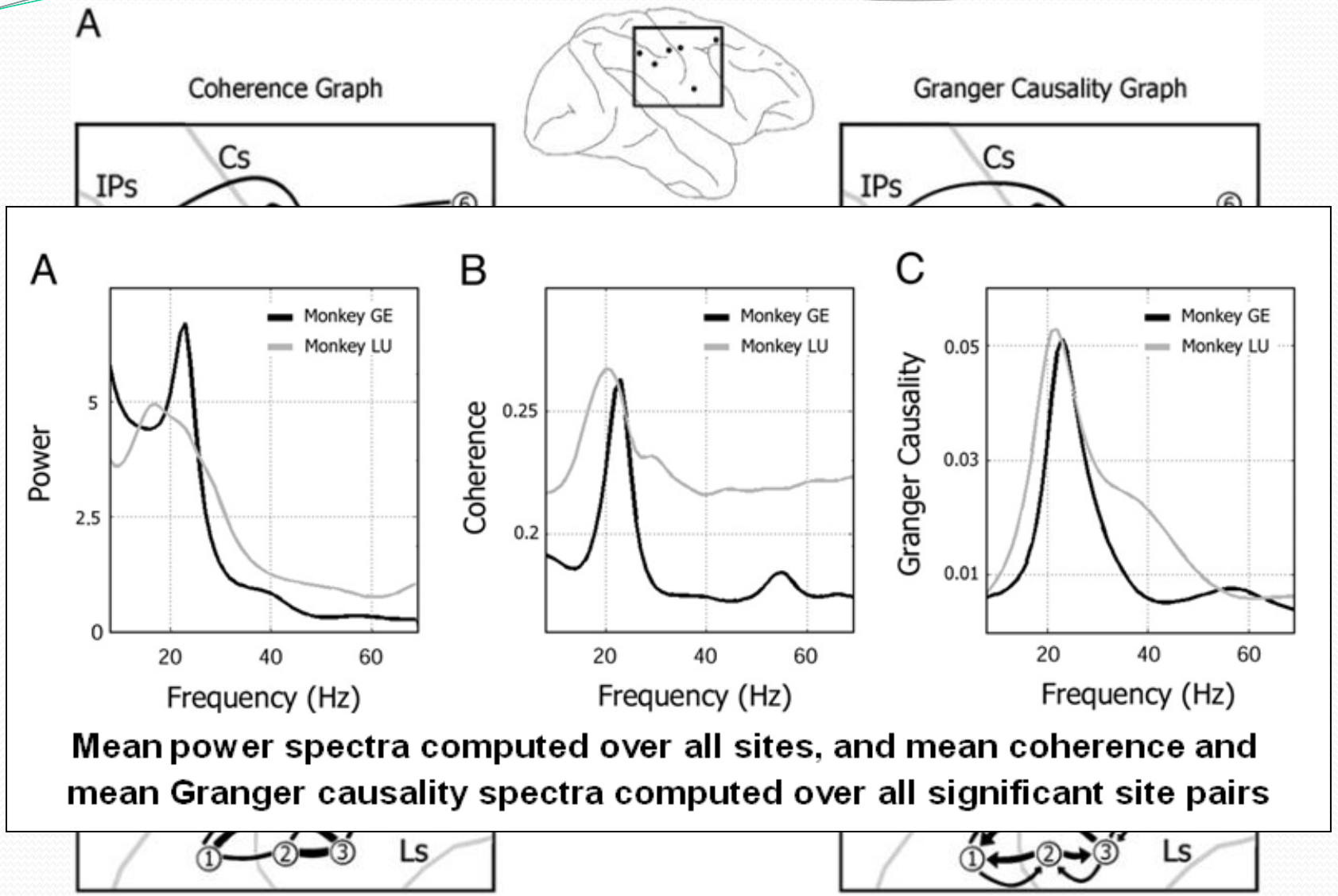
Granger Causality

- We get Granger causality spectral analysis by :

$$I_{k\to l}(f) = \frac{(Z_{kk} - Z_{lk}^2 / Z_{ll})\left|H_{lk}(f)\right|^2}{\left|S_{ll}(f)\right|}$$

and $$I_{l\to k}(f) = \frac{(Z_{ll} - Z_{kl}^2 / Z_{kk})\left|H_{kl}(f)\right|^2}{\left|S_{kk}(f)\right|}$$

where Z_{kk} , Z_{kl} , Z_{ll} and Z_{lk} are elements of the covariance matrix Z of the noise vector of the bivariate model, and S_{ll} and S_{kk} are the power spectra of time series obtained above.



Beta oscillations in sensorimotor cortical network: Directional influences revealed by Granger causality

Brovelli A et al. 2004, PNAS

Directed Transfer Function

- Kaminski and Blinowska (1991) proposed a multivariate spectral measure, called the Directed Transfer Function (DTF), which can be used to determine the directional influences between any given pair of channels in a multivariate dataset. DTF is an estimator that simultaneously characterizes the direction and spectral properties of the interaction between brain signals and requires only one multivariate autoregressive (MVAR) model to be estimated simultaneously from all the time series.

Directed Transfer Function

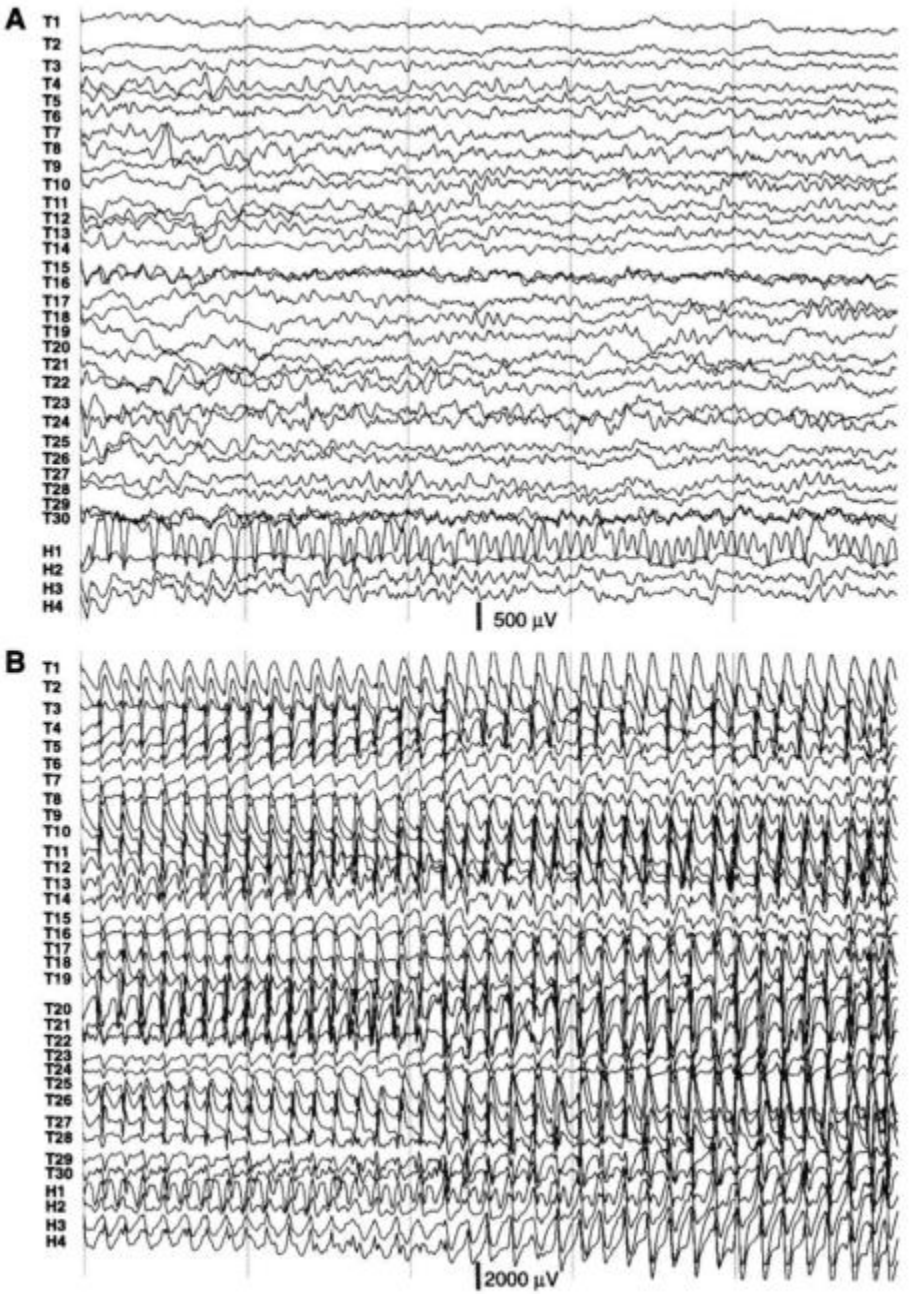
- The DirectedTransfer Function, representing the causal influence between *l*th channel and *k*th channel at the frequency f , is defined in terms of elements of the transfer matrix *H(f)*:

$$\theta_{lk}^{2}(f) = \left|H_{lk}(f)\right|^{2}$$

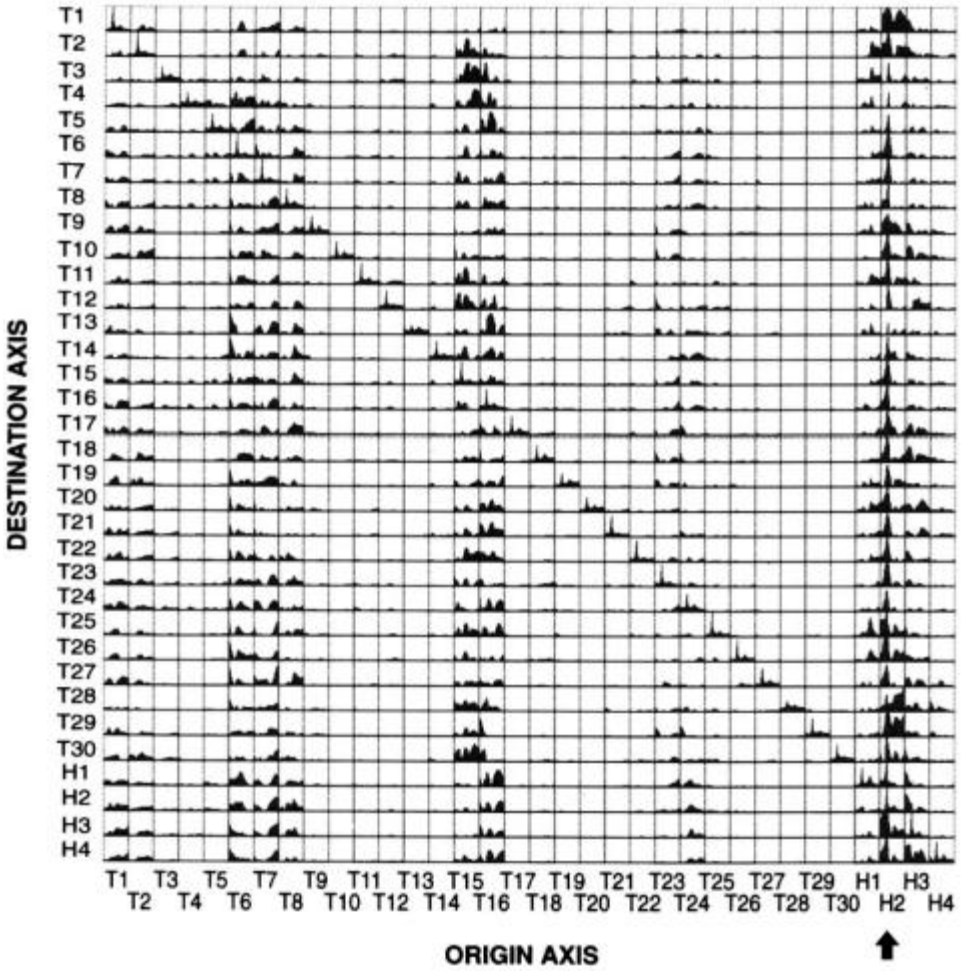
- And normalized DTF to compare the results obtained from cortical waveforms with different power spectra, by dividing each estimated DTF by the squared sums of all elements of the relevant row:

$$\gamma_{lk}^{2}(f) = \frac{\left|H_{lk}(f)\right|^{2}}{\sum_{m=1}^{N}\left|H_{lm}(f)\right|^{2}}$$

Application of the Directed Transfer Function Method to Mesial and Lateral Onset Temporal Lobe Seizures.

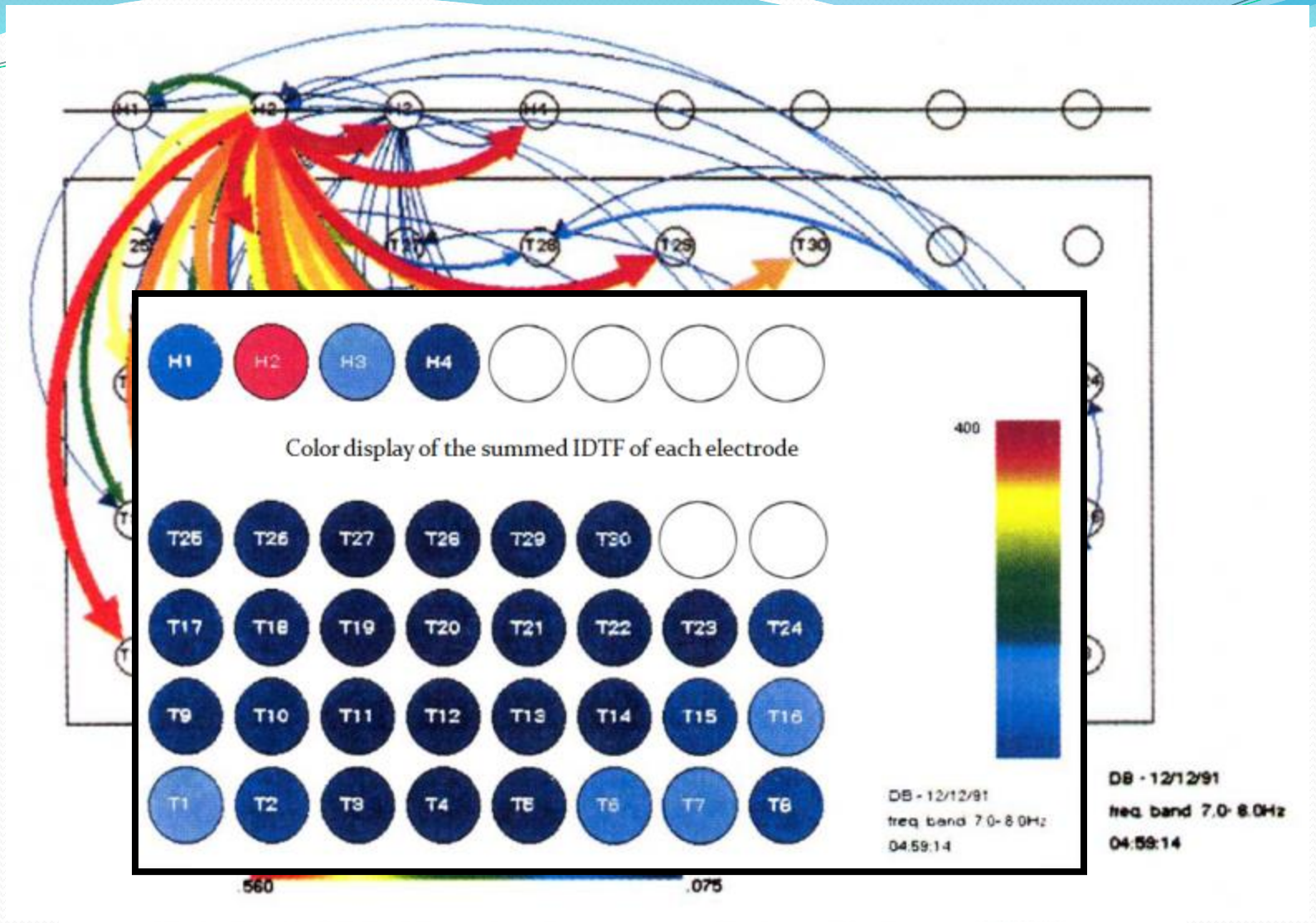


A: Mesial onset of the seizure near the depth array.
B: 27 seconds after A, where rhythmic 7.5Hz activity visible from all electrodes



DTF of B(left). Horizontal is scale of frequency 0-25Hz, vertical is scale of DTF 0-0.5.

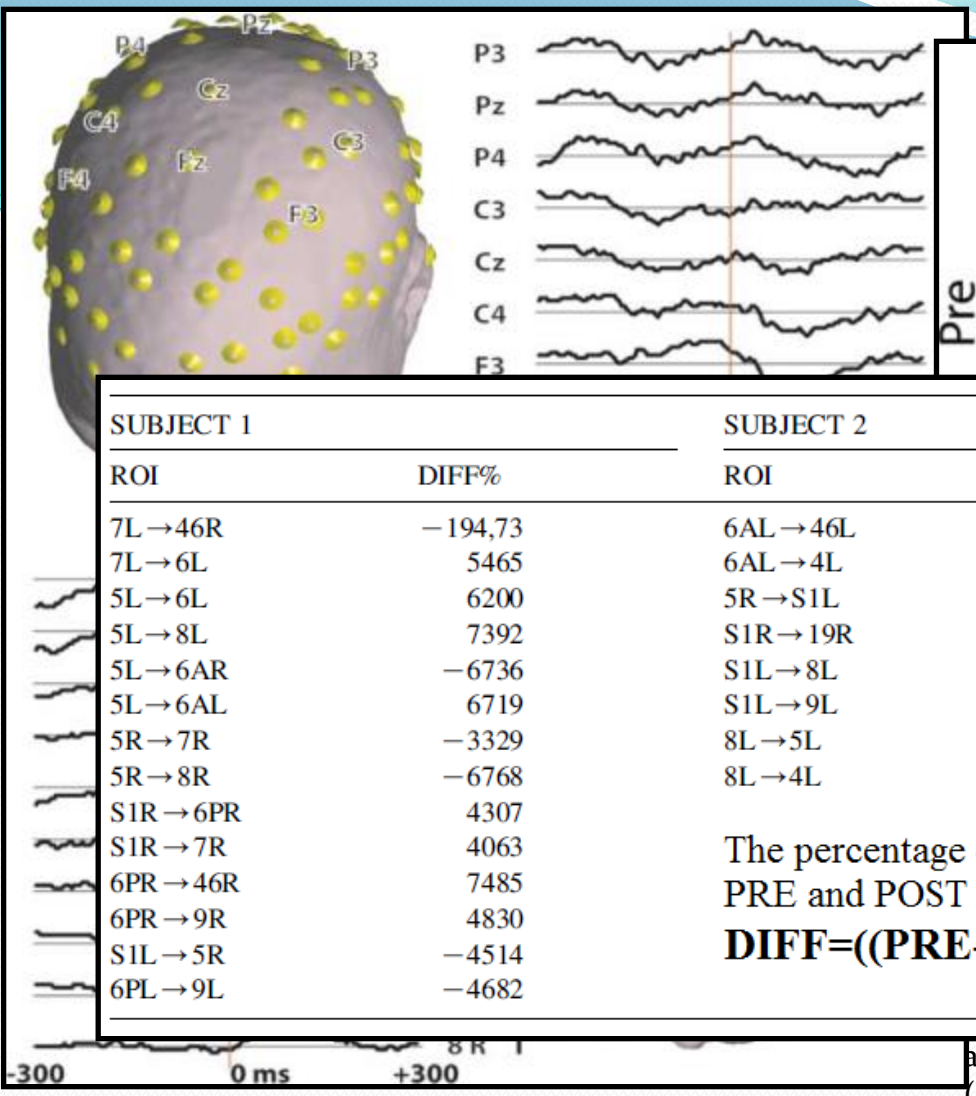
Piotr J. Franaszczuk et al., 1998, Brain Topography

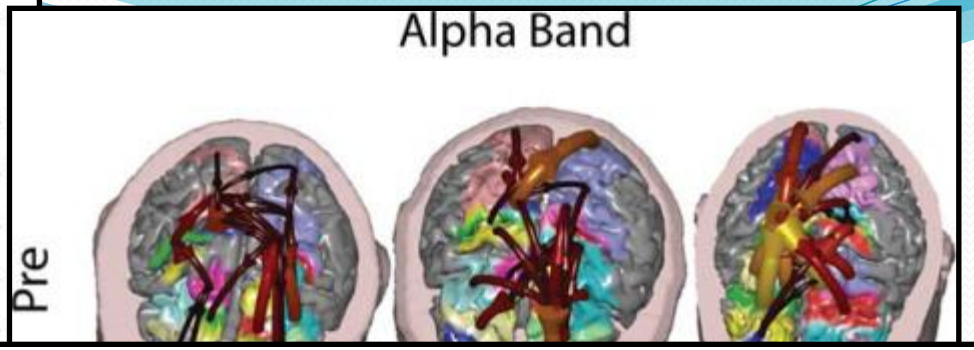


Integrated DTF of 7-8Hz

Application of the Directed Transfer Function Method to Mesial and Lateral Onset Temporal Lobe Seizures.

Piotr J. Franaszczuk et al., 1998, Brain Topography





SUBJECT 1		SUBJECT 2		SUBJECT 3	
ROI	DIFF%	ROI	DIFF%	ROI	DIFF %
7L→46R	−194,73	6AL→46L	4462	4R→46R	−137,51
7L→6L	5465	6AL→4L	6055	4R→5L	3122
5L→6L	6200	5R→S1L	−101,95	4R→8L	3831
5L→8L	7392	S1R→19R	−3241	6PL→6L	−3188
5L→6AR	−6736	S1L→8L	−3838	6PL→S1L	2635
5L→6AL	6719	S1L→9L	−5404	4L→ 5R	8359
5R→7R	−3329	8L→5L	3098		
5R→8R	−6768	8L→4L	6105		
S1R→6PR	4307				
S1R→7R	4063				
6PR→46R	7485				
6PR→9R	4830				
S1L→5R	−4514				
6PL→9L	−4682				

The percentage differences of the computed DTF values between the PRE and POST periods.

DIFF=((PRE-POST)/PRE)X100

and following the movement onset, for the 3 subjects, in the alpha (8–12 Hz) frequency band.

Top: a selection of the ERPs gathered from the standard electrode.
Bottom: The current density waveforms, represented for some selected ROIs on the realistic cortex.
The onset of the electromyographic (EMG) signal for the start of **the movement of the right finger** is at the oms.

Assessing cortical functional connectivity directed transfer function.

Piotr J. Franaszczuk et al., 1998, Brain Topography

Modification of DTF

- Full frequency Directed Transfer Function (ffDTF), in which a new normalization procedure for DTF was used. The ffDTF is defined as:

$$\gamma_{lk}^{2}(f) = \frac{\left|H_{lk}(f)\right|^{2}}{\sum_{f}\sum_{m=1}^{N}\left|H_{lm}(f)\right|^{2}}$$

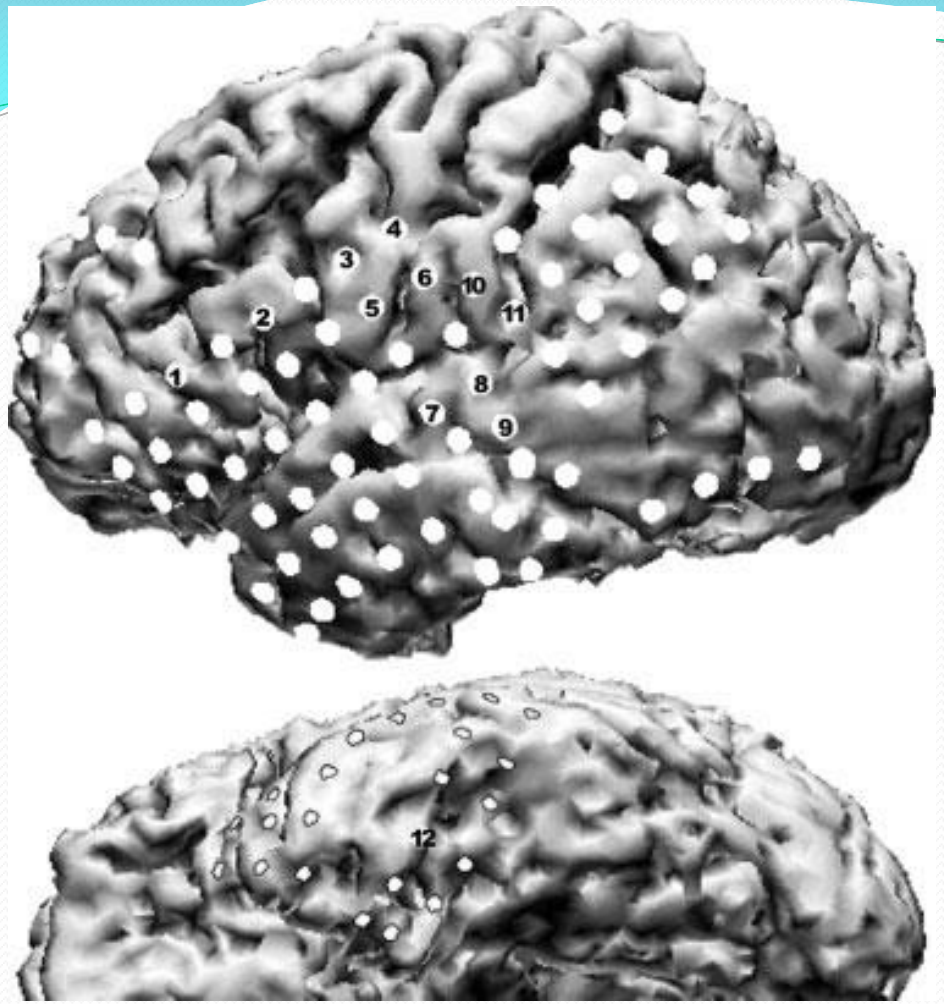
- The summation (or integration) over the whole frequency band assures that the denominator of the expression does not change with frequency. Spectral properties of ffDTF depend only on the outflow from that channel.

Modification of DTF

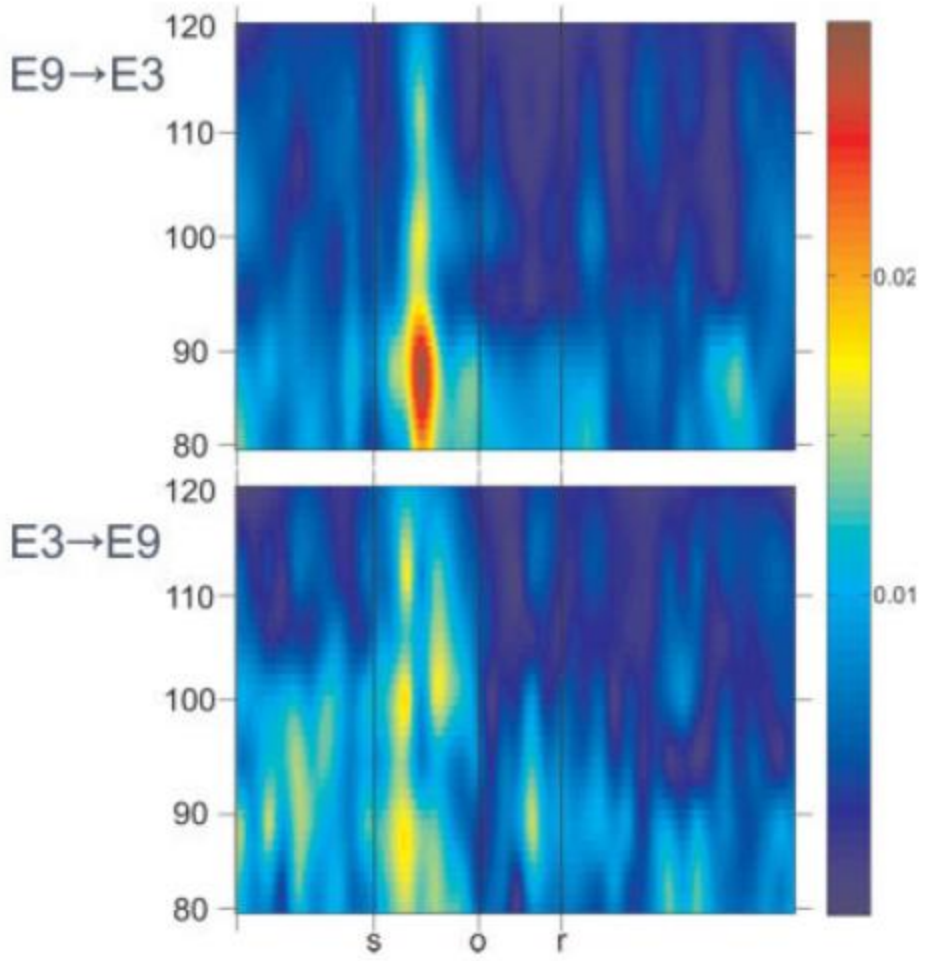
- Multiplying ffDTF by partial coherence we emphasize only direct connections. The new function is given by:

$$\delta_{lk}(f) = \chi_{lk}(f)\gamma_{lk}(f)$$

- We called the function obtained this way a direct Directed Transfer Function (dDTF). It combines information from partial coherence function with information about direction of influence in one measure.



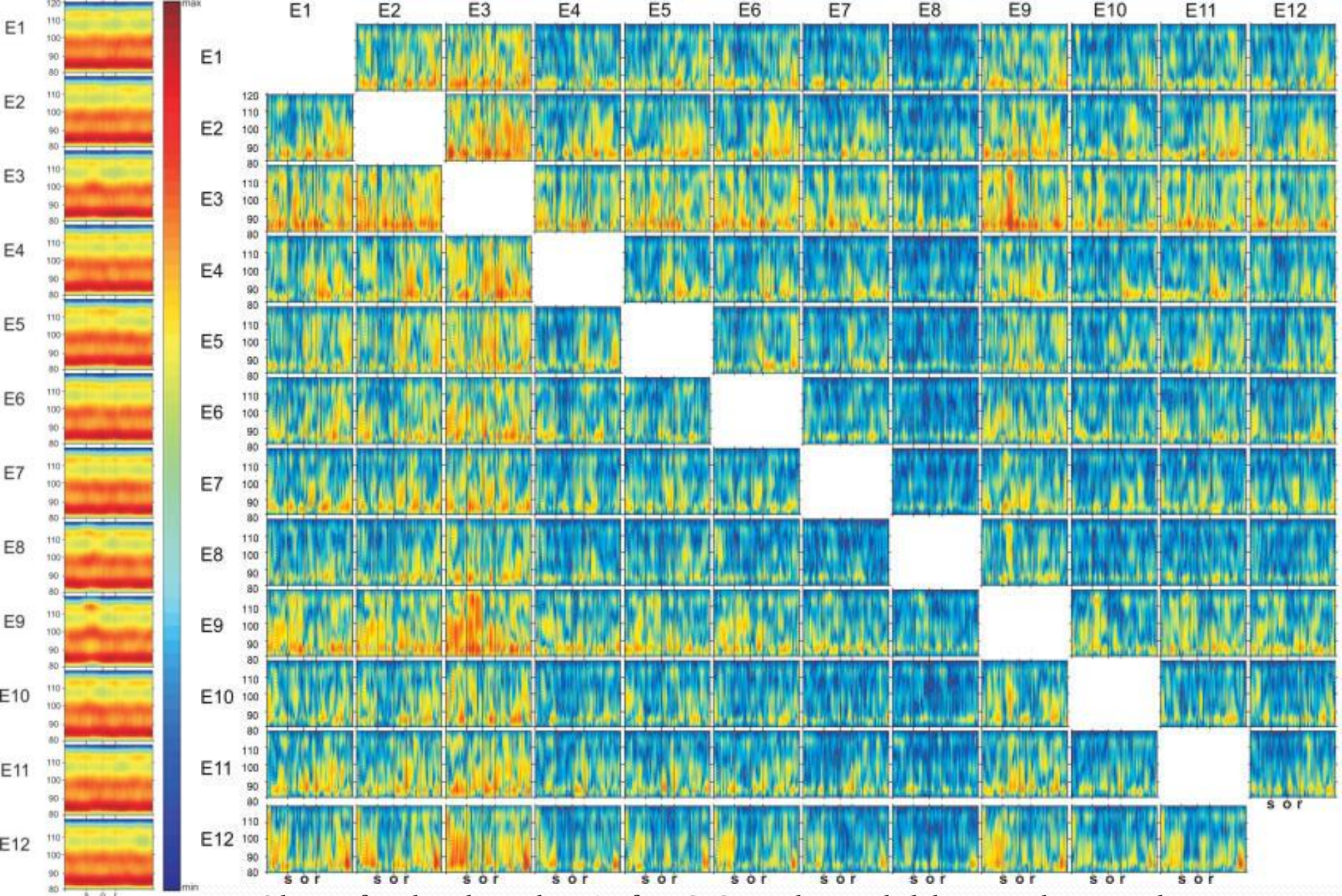
Positions of electrodes for ECoG recording. White discs indicate electrodes implanted for clinical purposes. Numbered discs indicate recording sites analyzed for this study.



Time-frequency plots of splined/smoothed Short time dDTF for between two channels (E3 and E9 in left), showing the entire analyzed frequency range. Horizontal axis is time with vertical lines demarcating stimulus onset (s), stimulus offset (o), and response onset (r).

Dynamics of Event-Related Causality in Brain Electrical Activity based on ECoG by Short time dDTF

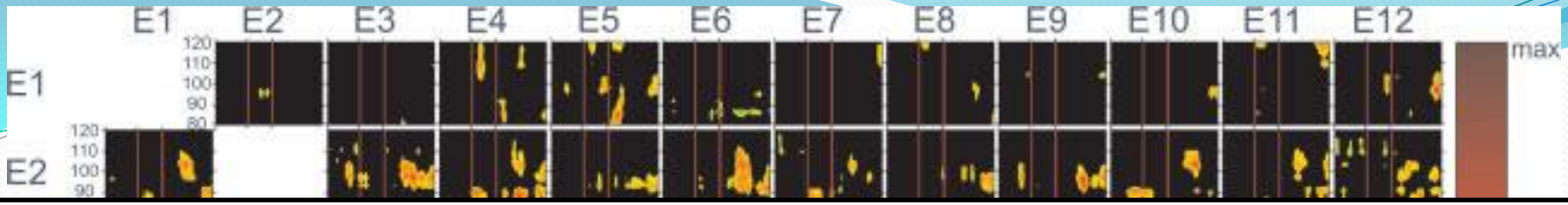
Anna Korzeniewska et al., 2008, Human Brain Mapping

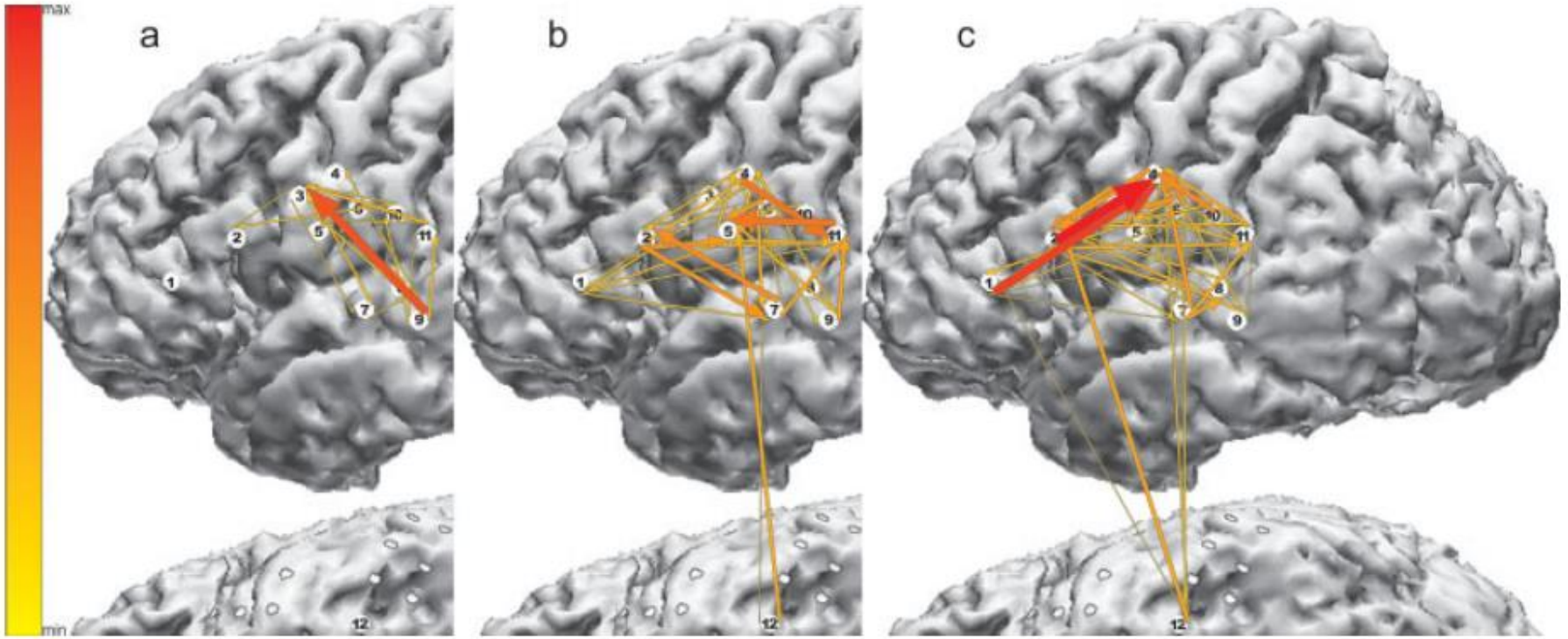


Power spectra

SdDTF of twelve-channel MVAR for ECoG signals recorded during auditory word repetition.

Anna Korzeniewska et al., 2008, Human Brain Mapping





Integrals of ERC for frequency range 82 – 100 Hz calculated for three stages of auditory word repetition task

Statistically significant event-related changes in SdDTF, referred as **Event Related Causality**

Anna Korzeniewska et al., 2008, Human Brain Mapping

Phase directionality index

- Phase directionality index is a nonlinear approach that is firstly developed by Rosenblum and Pikovsky to describe characteristics of coupling between two oscillatory systems from their time series
- It is based on the basic idea that weak coupling affects the phase of the system first rather than the amplitude.

Weak coupling:How it works

Phase directionality index

- Instantaneous phase $\phi_i(t_n)$ of time series are obtained by Hilbert transform:

$$y_i(t) = \mathrm{H}\big(x_i(t)\big) = pv \cdot \frac{1}{\pi}\int_{-\infty}^{\infty} \frac{x_i(t')}{t-t'}\,dt'$$

where *pv* indicates that the Cauchy principal value is taken in the integral, and $y_i(t)$ represents the imaginary part of the complex analytic signal $(z_i(t) = x_i(t) + jy_i(t) = A_i(t)e^{j\phi_i(t)})$.

- Coupling model between two time series is constructed as differential equations:

$$\dot{\phi}_1(t) = \omega_1 + G_1\big(\phi_1(t), \phi_2(t)\big) + \xi_1(t)$$
$$\dot{\phi}_2(t) = \omega_2 + G_2\big(\phi_1(t), \phi_2(t)\big) + \xi_2(t)$$

where w_i [illegible]gnals, and G_i are functions describing the coupling between them.

Phase directionality index

- For digital signals, difference equations defined model is more conveniently to be considered:

$$\Delta_1(t_n) = F_1[\phi_1(t_n),\ \phi_2(t_n)] + \eta_1$$
$$\Delta_2(t_n) = F_2[\phi_1(t_n),\ \phi_2(t_n)] + \eta_2$$

where $\Delta_1(t_n)$ is the increments of phase series $\phi_1(t)$. F1 and F2 could be estimated by trigonometric polynomials:

$$F_1 = \sum_{m,n}\left[a_{1,m,n}cos(m\phi_1 + n\phi_2) + b_{1,m,n}sin(m\phi_1 + n\phi_2)\right]$$
$$F_2 = \sum_{m,n}\left[a_{2,m,n}cos(m\phi_1 + n\phi_2) + b_{2,m,n}sin(m\phi_1 + n\phi_2)\right]$$

- Phase influence ($c_{1,2}^2$) and coupling directionality (d) are:

$$c_{1,2}^2 = \frac{1}{2\pi^2}\int_0^{2\pi}\int_0^{2\pi}\left(\frac{\partial F_{1,2}}{\partial \phi_{2,1}}\right)^2 d\phi_{1,2}\, d\phi_{2,1}$$

$$directiona\quad lity\ :$$

$$d = \frac{c_2 - c_1}{c_2 + c_1}\quad \begin{matrix} 1 \rightarrow 2\ when\quad d > 0 \\ 2 \rightarrow 1\ when\quad d < 0 \end{matrix}$$

Short time modification of Phase directionality index

- The estimation of coupling direction for pairwise short time series is defined as:

$$\hat{\delta} \equiv \hat{\gamma}_2 - \hat{\gamma}_1$$

where $\hat{\gamma}_2$ and $\hat{\gamma}_1$ are the short time correction of $c_{1,2}^2$:

$$\hat{\gamma}_1 = \hat{c}_1^2 - \sum_{m,n} n^2 \left(\hat{\sigma}^2_{\hat{a}_{1,m,n}} + \hat{\sigma}^2_{\hat{b}_{1,m,n}} \right)$$

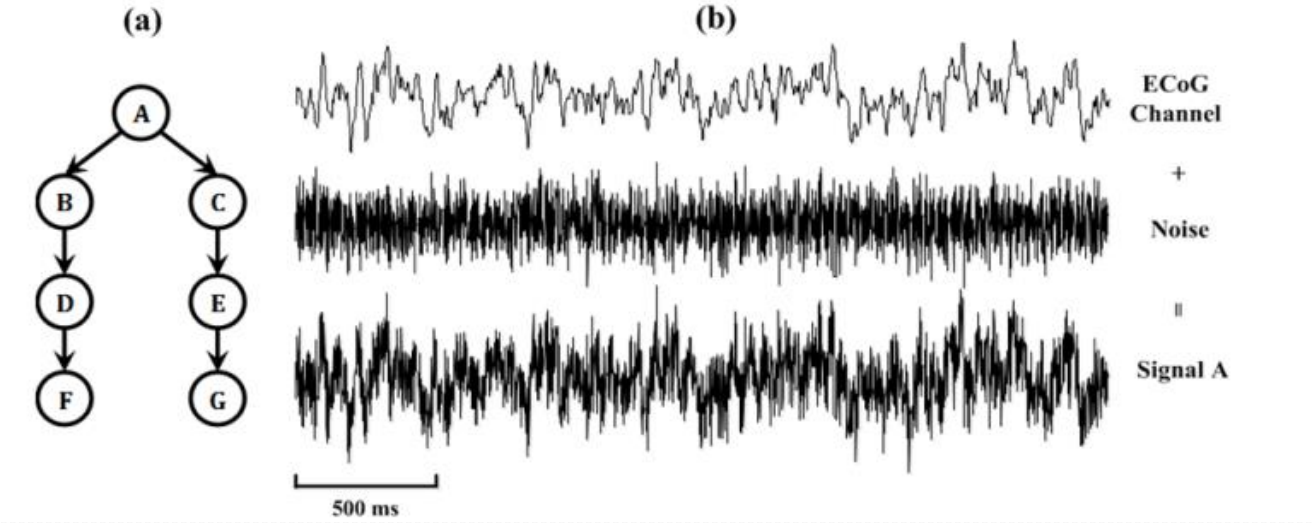
- The confidence interval for estimation of c_1^2 is defined as

$$\left[\hat{\gamma}_1 - \alpha \hat{\sigma}_{\hat{\gamma}_1}, \hat{\gamma}_1 + \beta \hat{\sigma}_{\hat{\gamma}_1} \right]$$

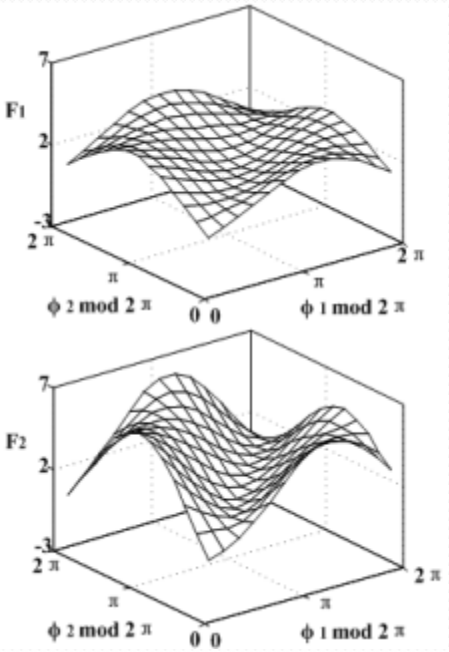
where $\hat{\sigma}_{\hat{\gamma}_1}$ is semiempirical obtained (not detailed):

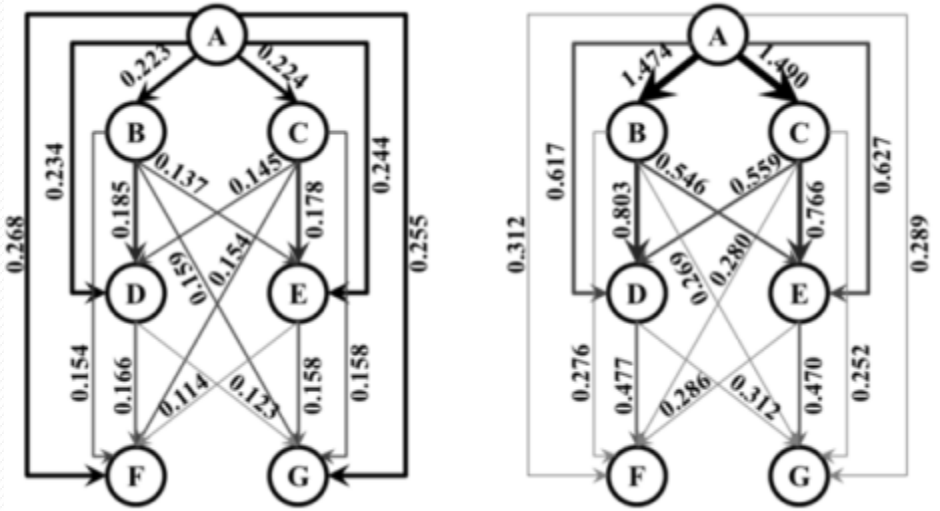
$$\hat{\sigma}^2_{\hat{\gamma}_1} = \begin{cases} \sum_{m,n} n^4 \left(\hat{\sigma}^2_{\hat{a}^2_{1,m,n}} + \hat{\sigma}^2_{\hat{b}^2_{1,m,n}} \right) & , \hat{\gamma}_1 \geq 5 \left(\sum_{m,n} n^4 \left(\hat{\sigma}^2_{\hat{a}^2_{1,m,n}} + \hat{\sigma}^2_{\hat{b}^2_{1,m,n}} \right) \right) \\ \frac{1}{2} \sum_{m,n} n^4 \left(\hat{\sigma}^2_{\hat{a}^2_{1,m,n}} + \hat{\sigma}^2_{\hat{b}^2_{1,m,n}} \right), & otherwise. \end{cases}$$

Simulation study of phase based directional Connectivity from Human ECoG



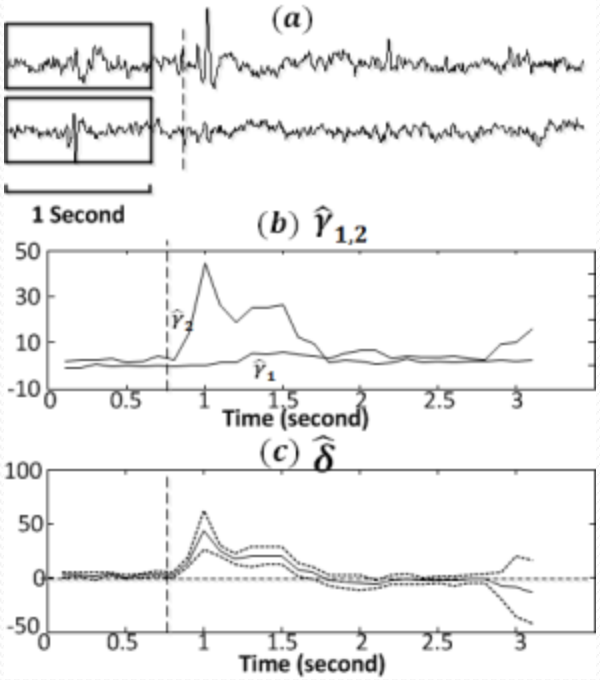
Simulation data are constructed from one channel of real ECoG recording with cascaded time delay and Gaussian noise.



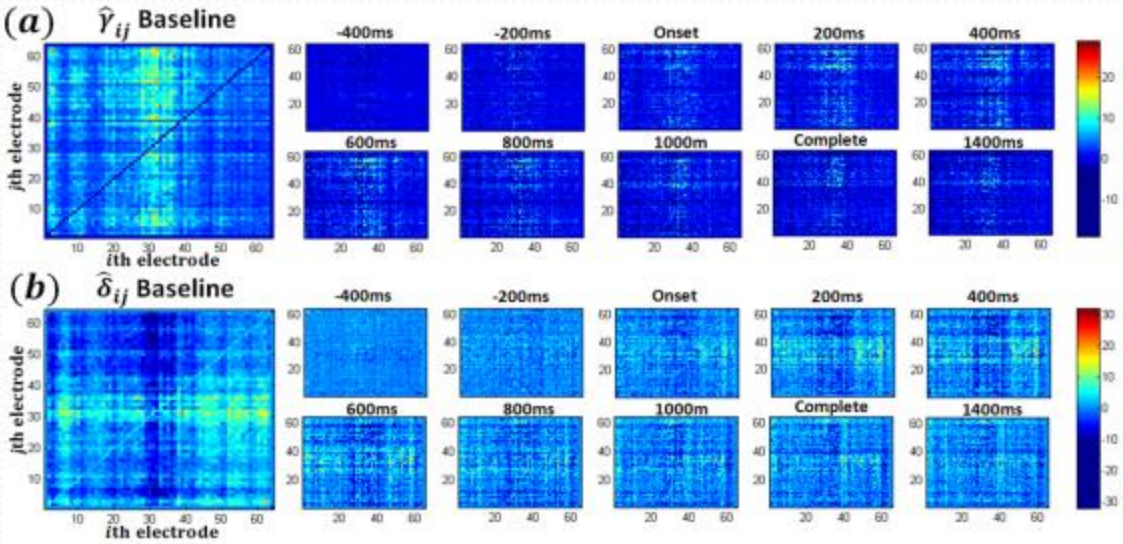


Left: Phase dependence function between signal A and signal B. Upper right: Simulation result of coupling directionality and its short time correction.

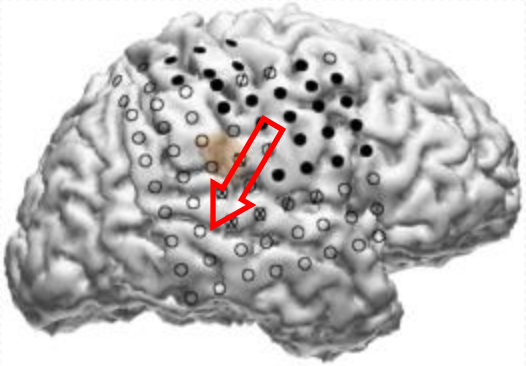
Computation of phase based dynamic directional connectivity mapping of human ECoG during hand open-close experiment:

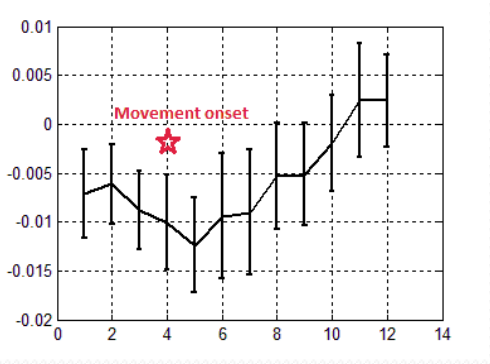


(a) ECoG recording (Channel 40 and channel 53) of after 0.15~300Hz bandpass filter and common average reference (CAR). (b) Short time correction of phase influence. (c) Short time correction of directionality during hand movement.



Normalized short time coupling direction index in 64-electrodes ECoG grid during hand movement, with window size 1000 ms.





Short time coupling directionality between motor cortex and sensory cortex in patient during hand movement, with frequency band 70~100Hz, windows 1250 ms & overlapping 1000 ms.

Time-varying Dynamic Bayesian Network

- In TVDBN, the conditional probability of observing a given value at time t given a value at previous time t–1 is $P(X^t \mid X^{t-1})$, a first order Markov model in which the state of X at time t depends only on its previous state.
- In the model, the distribution of temporal transitions can be described as a linear model: $X^t = A^t X^{t-1} + \varepsilon$, A^t_{ij} is the connectivity weight from the ith to the jth channel from time t – 1 to time t.

  The A^t term can be estimated at time t with:

Time-varying Dynamic Bayesian Network

- The A^t term can be estimated at time t with:

$$\hat{A}_{i.}^{t} = arg\min_{A_i^t \in R^{1\times N}} \frac{1}{T}\sum_{t^*=1}^{T} w^t(t^*)(x_i^{t^*} - A_i^t X^{t^*-1}) + \lambda \left\| A_i^t \right\|$$

where The parameter λ defines a regularization term that shrinks the sparseness of the connection matrix A. And the weight of an observation at time t^* is given by :

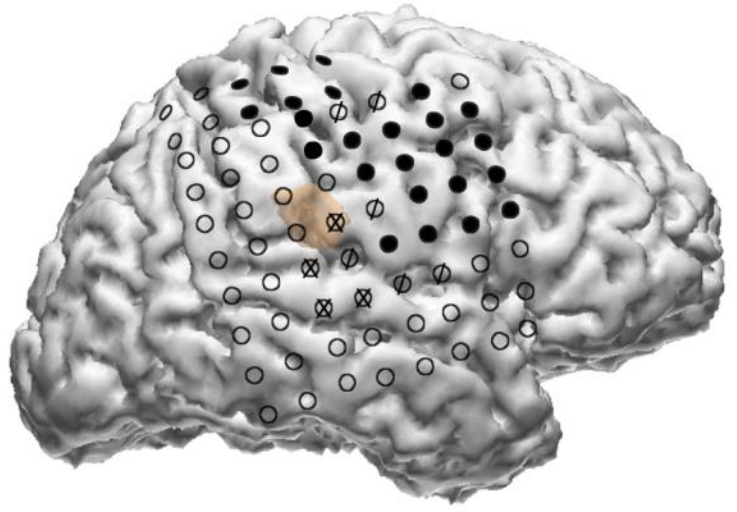
$$w^t(t^*) = \frac{K_h(t^* - t)}{\sum_{t^*=1}^{T} K_h(t^* - t)}$$

in which $K_h(\cdot) = e^{(-t^2/h)}$, a Gaussian kernel function.

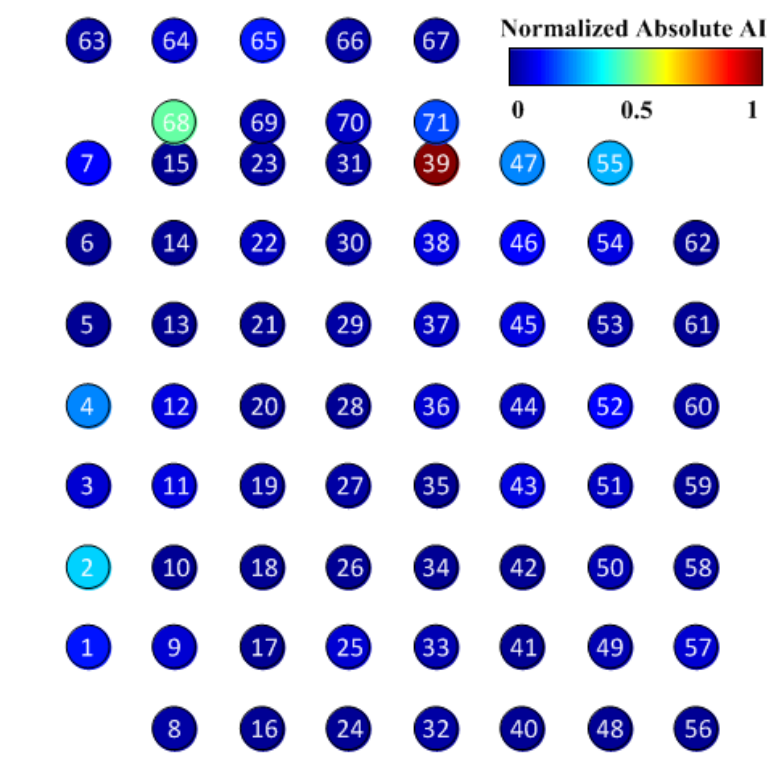
- The network can be solved as a weighted regression problem by least squares.

Time-varying Dynamic Bayesian Network

- Implementation TVDBN on ECoG data.

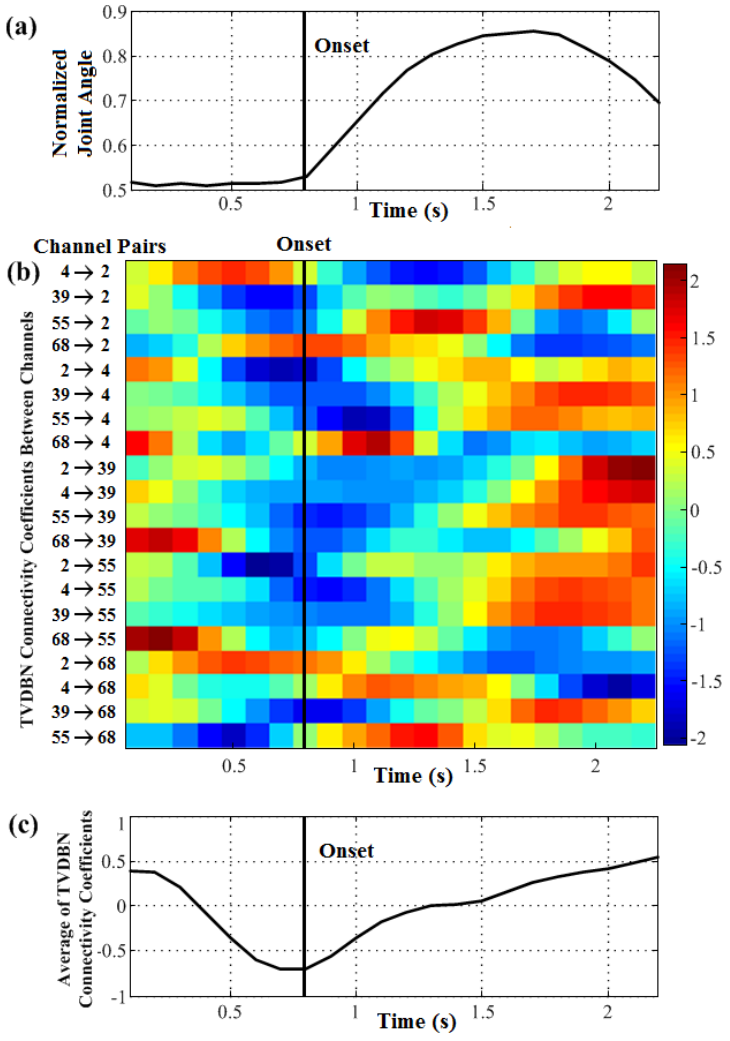


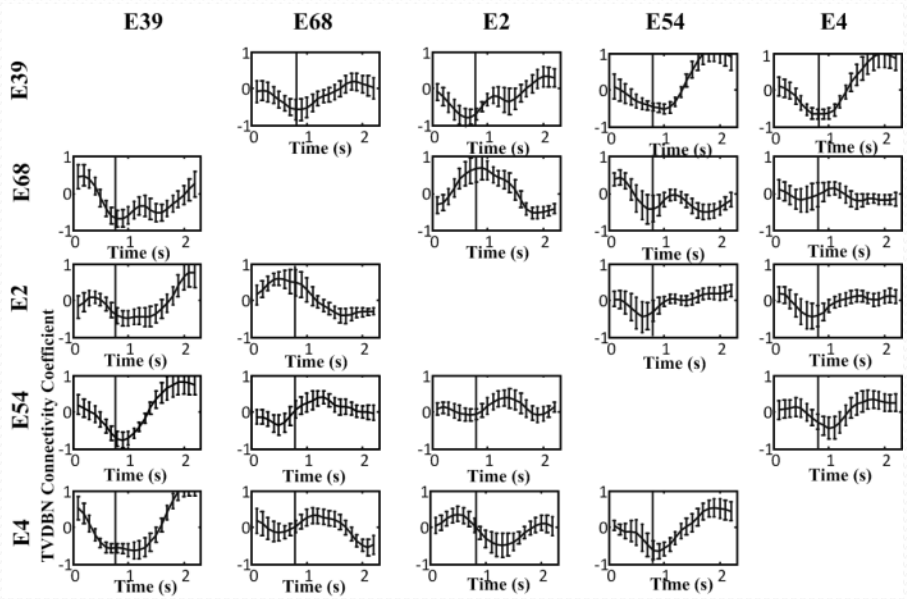
ECoG grids in human brain



Select electrode subsets by their correlation with hand movements: Activation Index

Time-varying Dynamic Bayesian Network

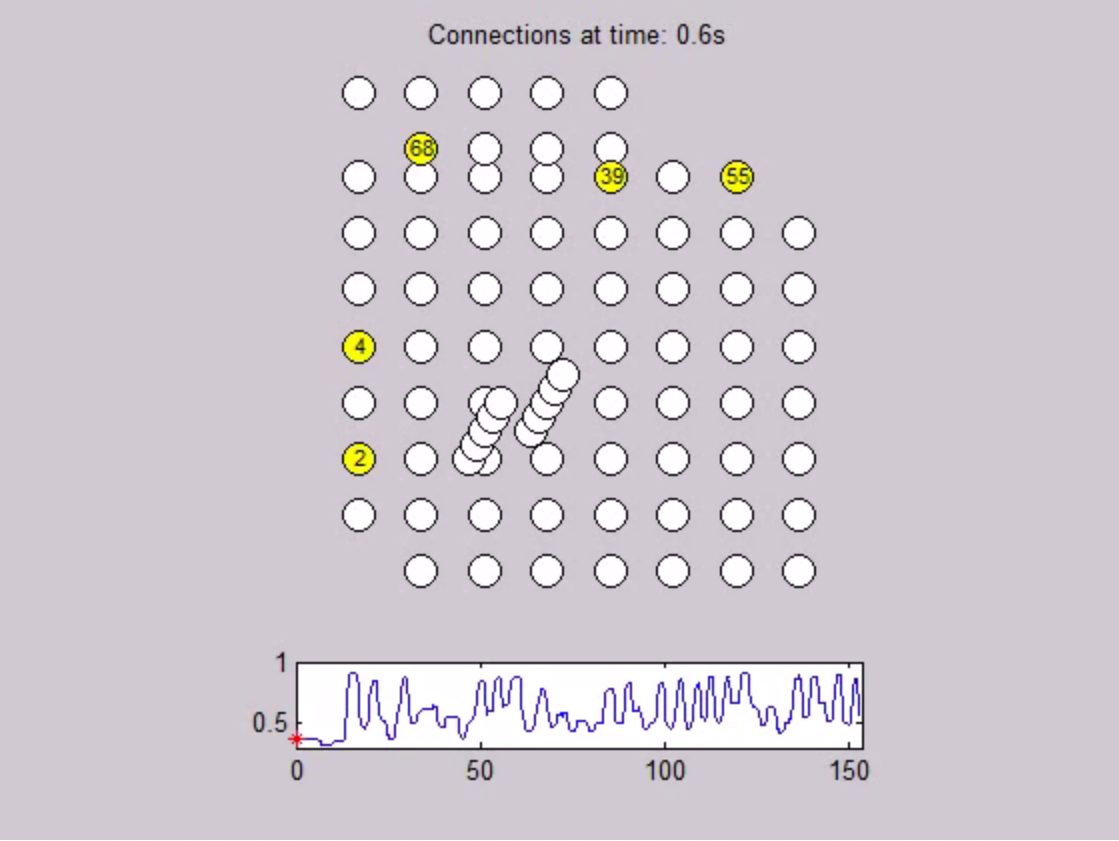




Connections between electrodes and their variances across movement trials.

(a) Hand joint angle. (b) Connections between ECoG electrodes by TVDBN during hand movements. (3) Average connections

Time-varying Dynamic Bayesian Network



Up: Connections between electrodes.
Down: Hand joint angle.

Thank you for your attention