Proteomics Course

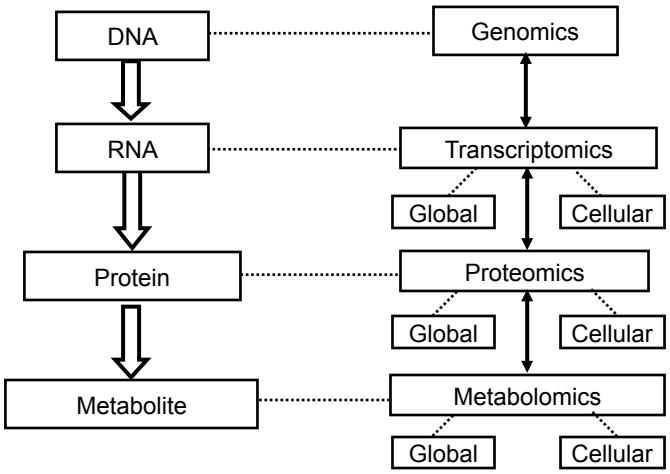
LECTURE-8
Proteomics and Systems Biology

Dr. Sanjeeva Srivastava
IIT Bombay

Lecture outline

- Proteomics
- Systems Biology

Omics

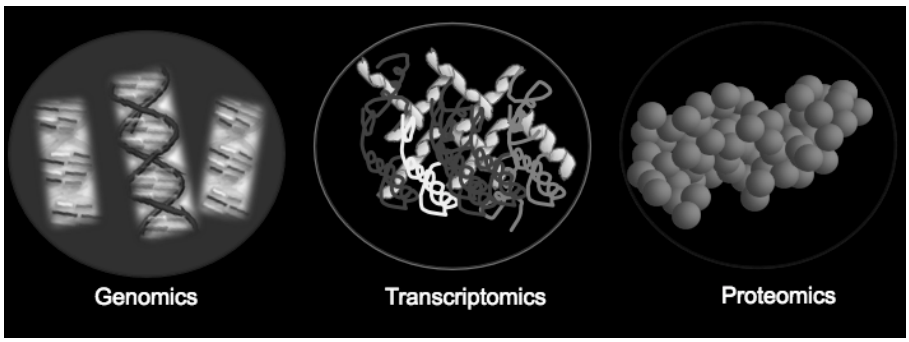


Proteomics

Proteomics

- Proteome: set of all the PROTEins expressed by a genOME
- Proteomics: study of full set of proteins encoded by a genome for their expression, localization, interaction and post-translational modifications

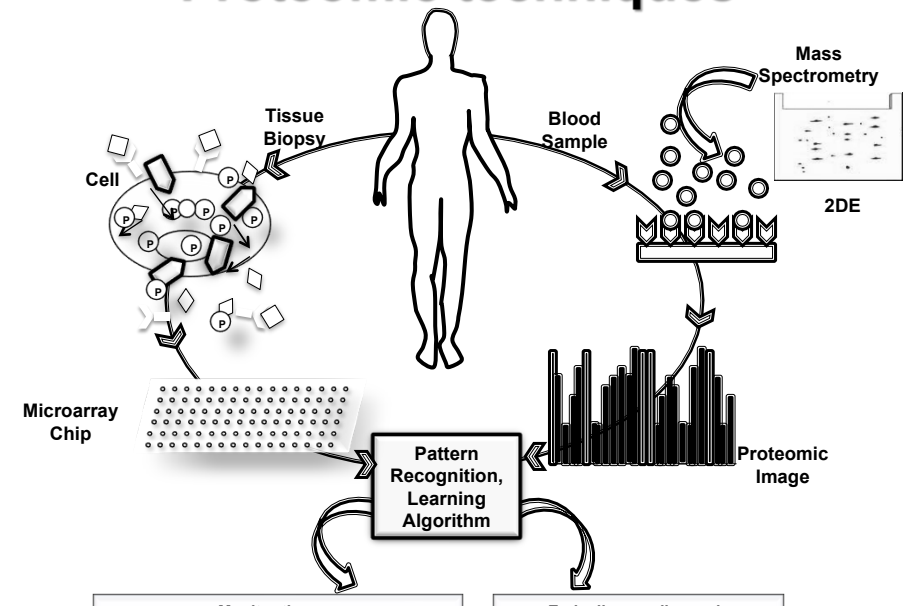
Significance of Proteomics



Proteomic techniques

Gel-based methods	Gel-free MS	Mass Spectrometry	Interactomics	Structural Proteomics
• SDS-PAGE • 2-DE • DIGE • BN-PAGE Staining • Coomassie Blue • Silver • Fluorescent (Sypro ruby) • PTM stains (Pro-Q Diamond) (Pro-Q Emerald) • Multiplex staining	• SILAC • CDIT • ICAT • VICAT • MCAT • QUEST • iTRAQ • GIST • [^{18}O] water • ICPL • AQUA • QCAT • SISCAPA • COFRADIC • MudPIT	Ionization • MALDI • ESI Mass analyzer • Quadrupole • Ion trap • TOF • FT-ICR Mass spectrometers • MALDI-TOF • Tandem MS (MS/MS) • DIOS • SELDI-TOF	• IP • Yeast two hybrid Protein microarrays • Antibody based • NAPPA • MIST Detection - Labelled - Label-free • SPR • Carbon nanowires	• X-ray crystallography • NMR • TROSY • Electron crystallography • Electron tomography Label-free • Atomic Force Microscopy • CD

Proteomic techniques



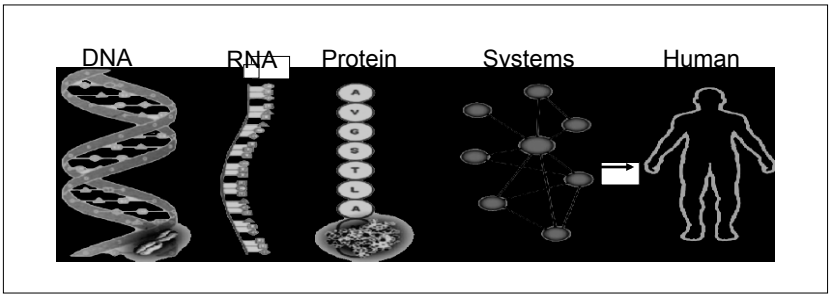
Systems Biology

Systems Biology

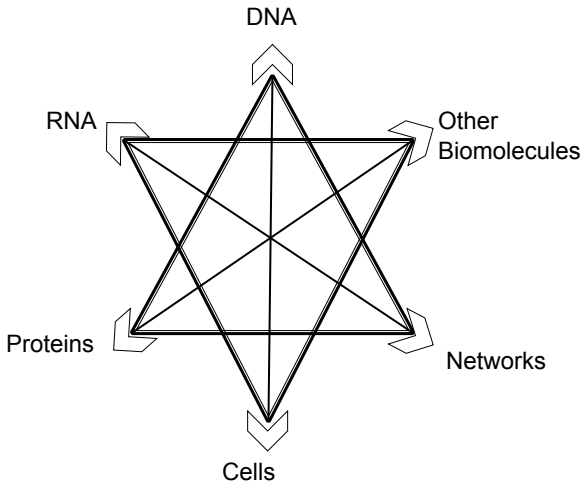
- Examination of a biological entity as an integrated system, rather than study of its individual characteristic reactions and components

Systems Biology

- System level understanding of biological networks
- Common elements of systems biology
  - Networks
  - Modeling
  - Computation
  - Dynamic properties

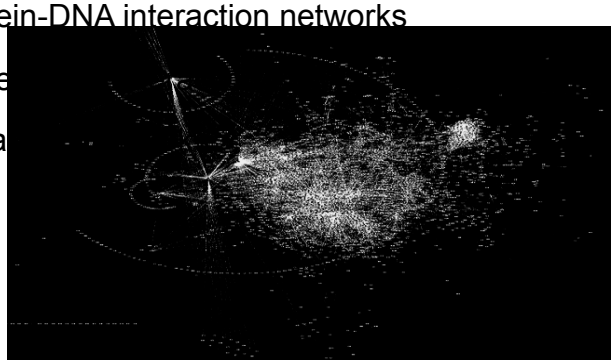


Biological Systems

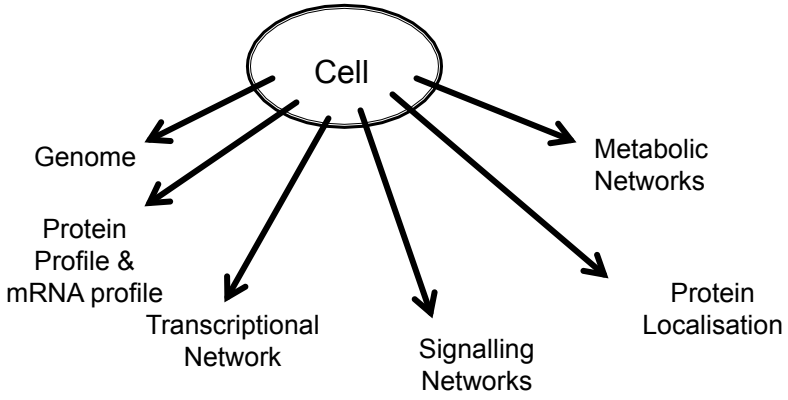


Biological networks

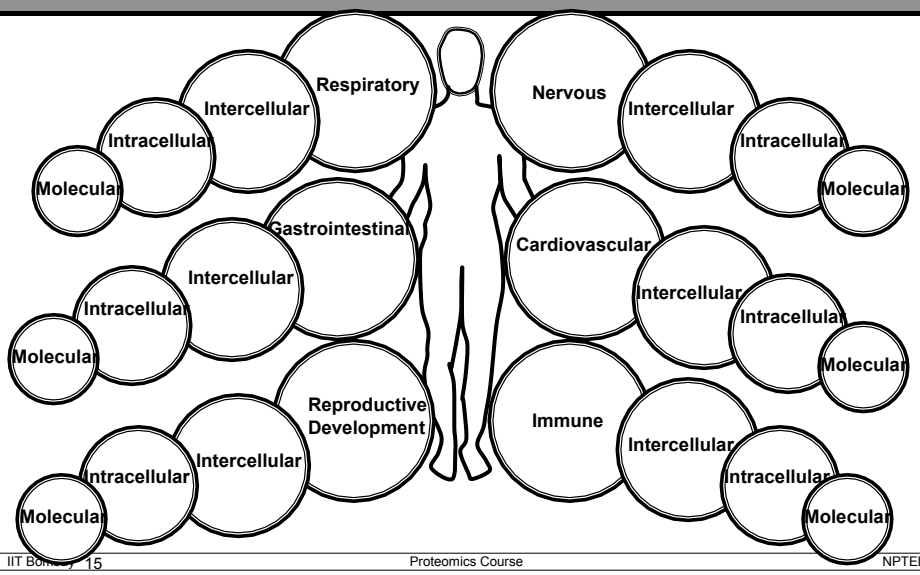
- Protein-protein interaction networks
- Gene regulatory networks
- Protein-DNA interaction networks
- Prote
- Meta



Ingredients of Systems Biology

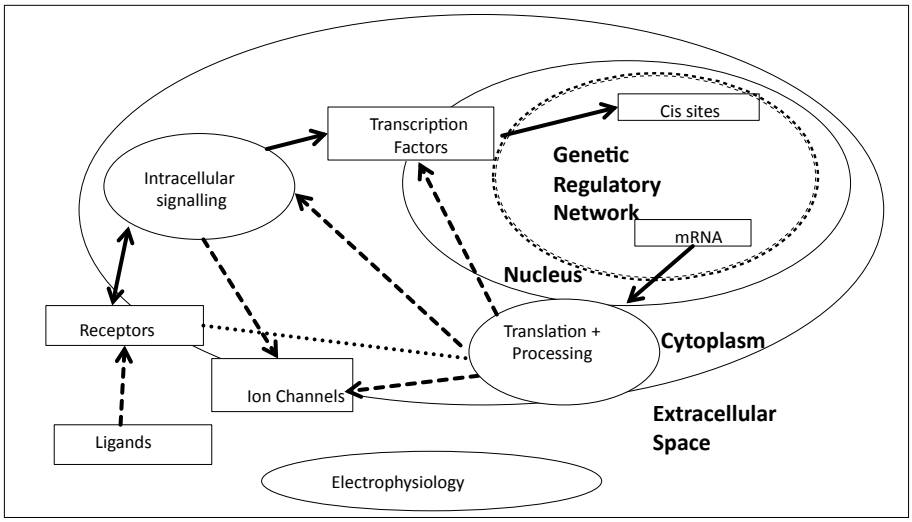


Levels of Study for System Biology



Need for Systems Biology

IPG strip



Aim of Systems Biology

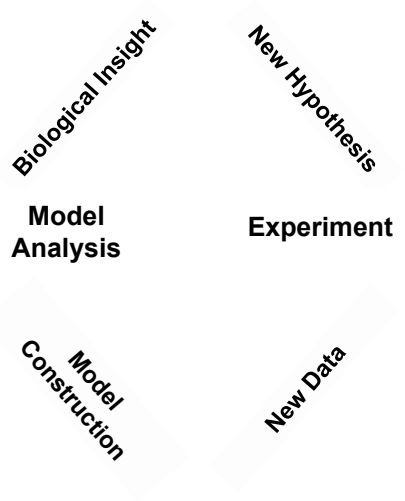
- Understanding biology in “holistic” rather than the “reductionist” approach
- Quantitate the qualitative biological data
- To make biology a predictive science

Systems Biology Approach

- Systems biology involves:
- Experimental data set collection
- Mathematical models

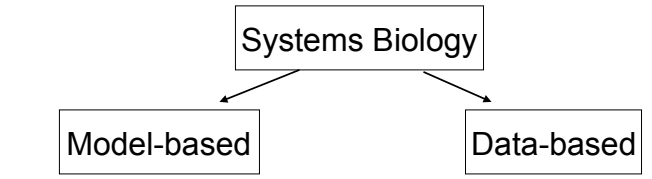
Systems Biology Approach (2)

IPG strip



Systems Biology: Different Approaches

Systems Biology: Distinct Approaches



Model-based	Data-based
Prior information implemented	Finding new phenomena
Computation modeling and simulation tools	Datasets (“omic”)

Studying Systems Components

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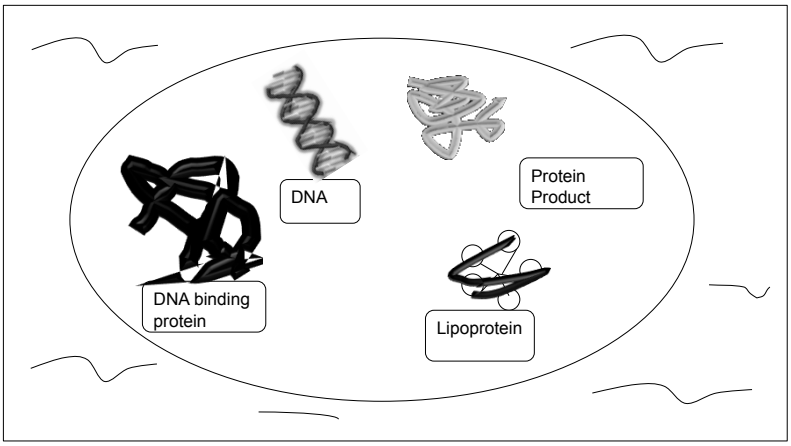
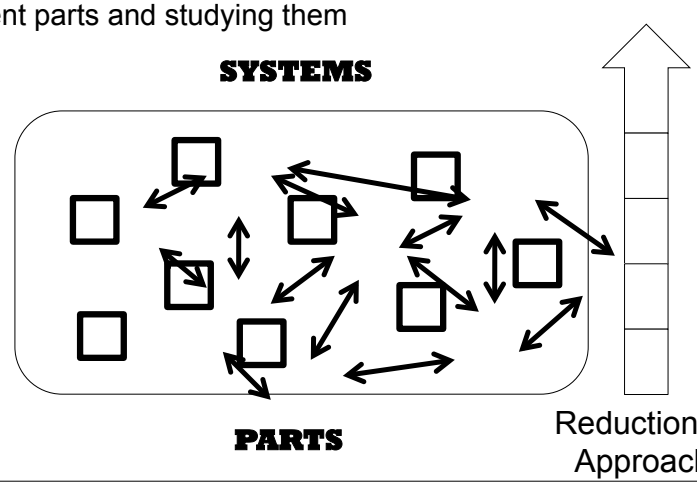


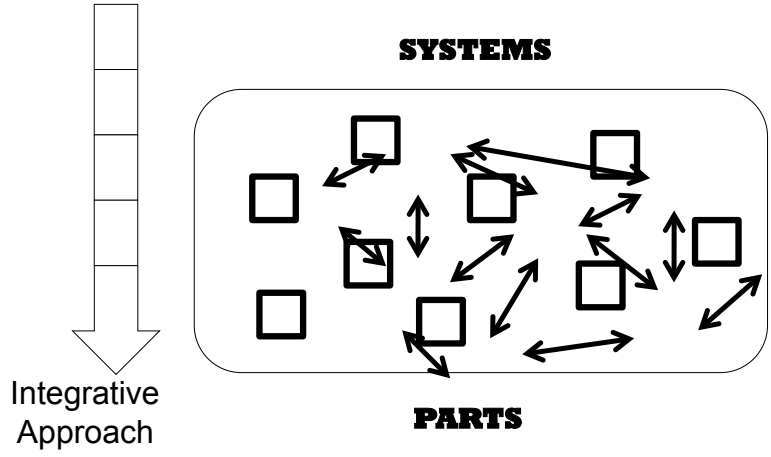
Systems Biology: Distinct Approaches

Reductionist Approach: Disintegrating the system into its component parts and studying them



Systems Biology: Distinct Approaches

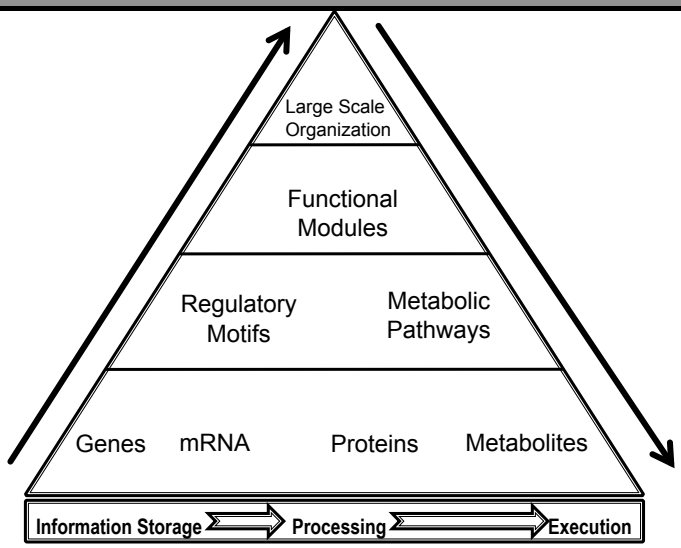
Integrative Approach: Integrating the study of individual components to form conclusions about system



Systems Biology Triangle

Systems Information

IPG strip



Systems Information

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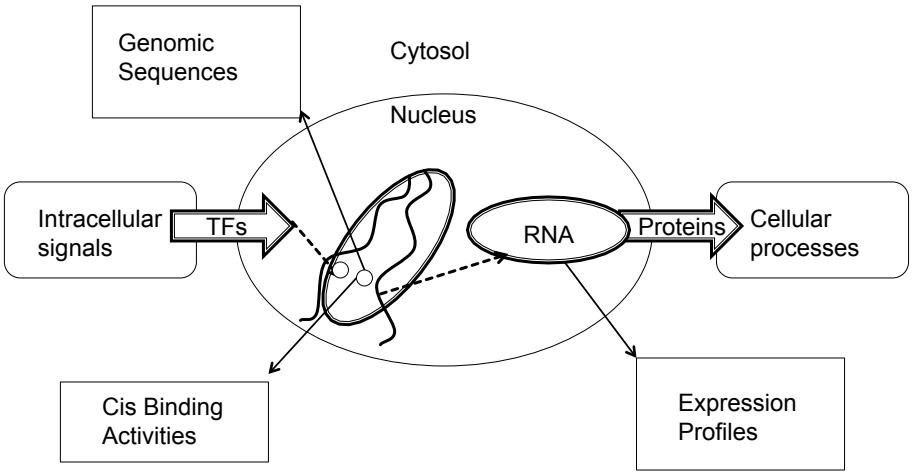
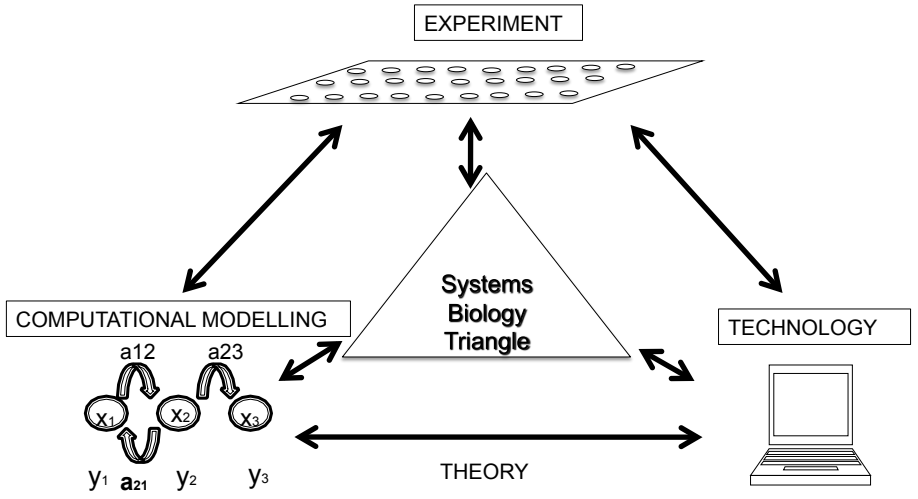


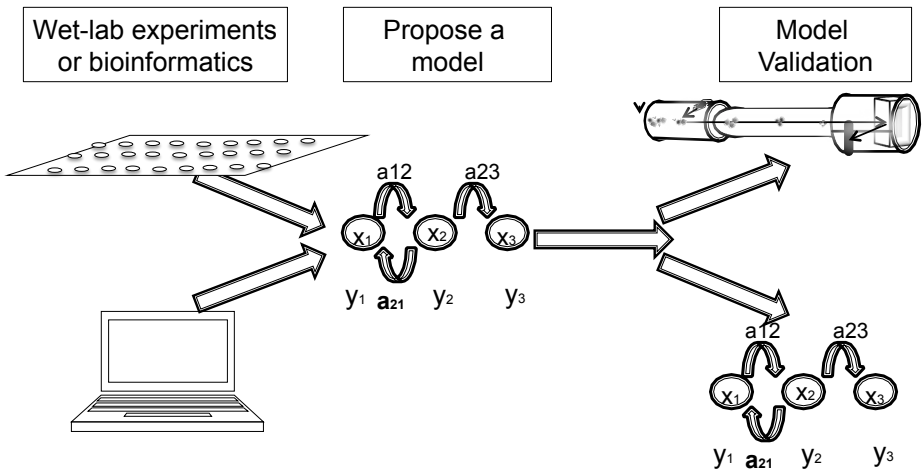
Approach

- Extraction and mining of complex & quantitative biological data
- Integration and analysis of data for development of mechanistic, mathematical & computational models
- Validation of models by refining and re-testing

Systems Biology Triangle

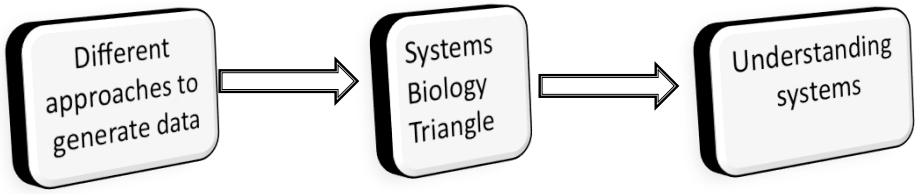


Systems Biology Triangle (2)

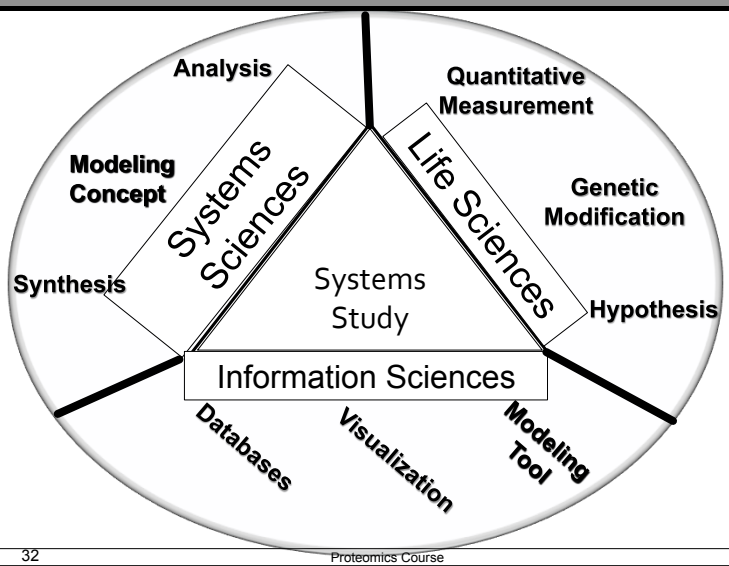


Systems Study

IPG strip



Systems Study and Model building



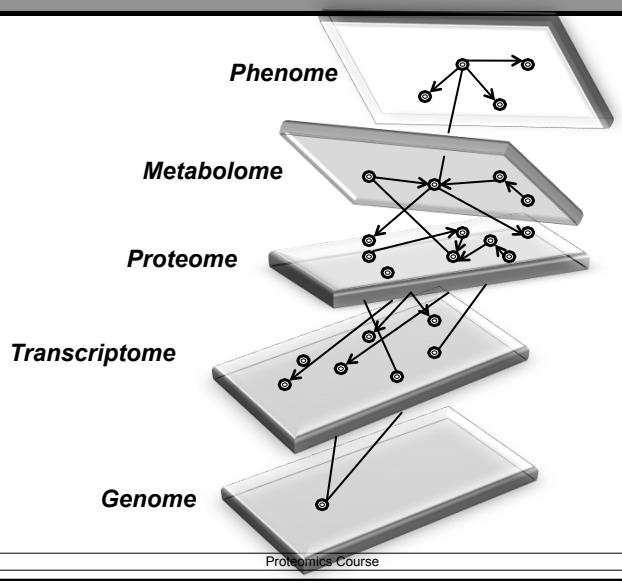
Technologies to Study Systems Biology

Systems Biology: Technologies employed

- HT-DNA sequencing, SNPs
- Microarrays, SAGE, RNA-Seq
- MS, 2D-PAGE, Protein chips, Yeast-2-hybrid
- NMR, X-ray

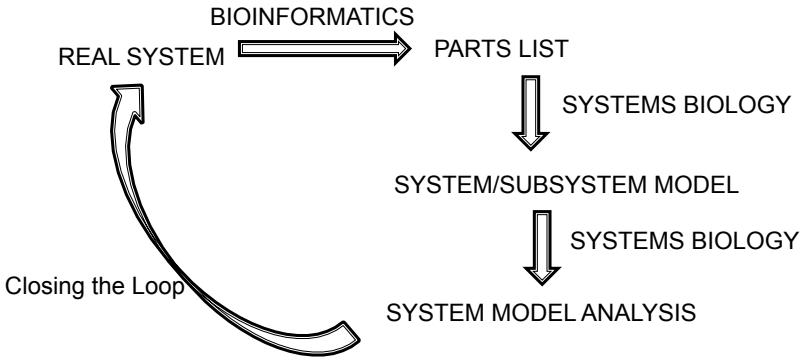
Technologies employed in Systems Biology

IPG strip

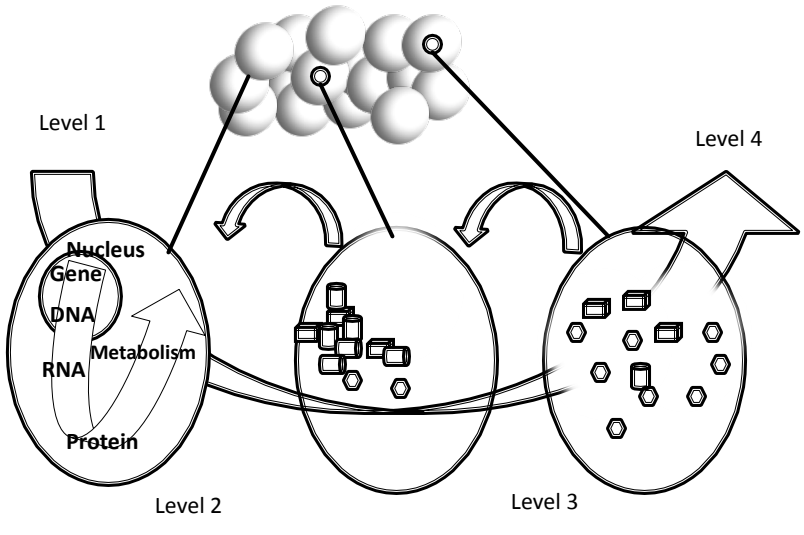


Modeling Biological Networks

Building Models in Systems Biology



Building Models in Systems Biology



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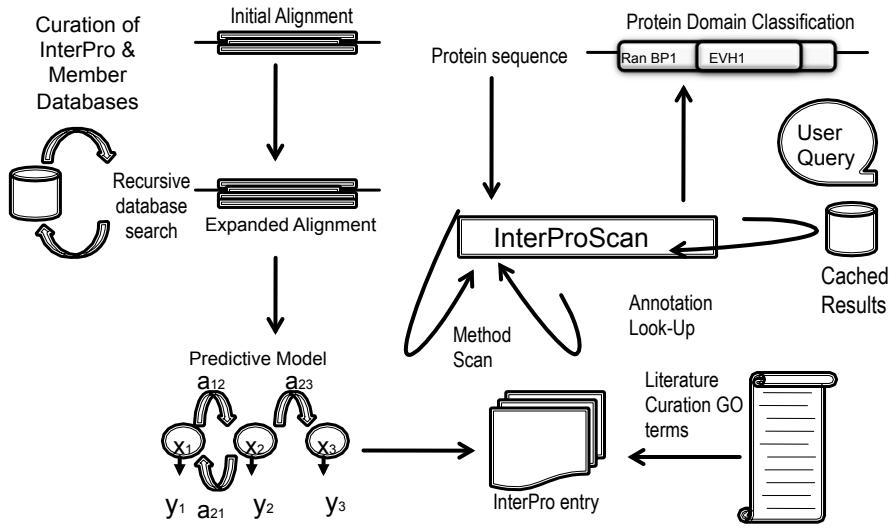
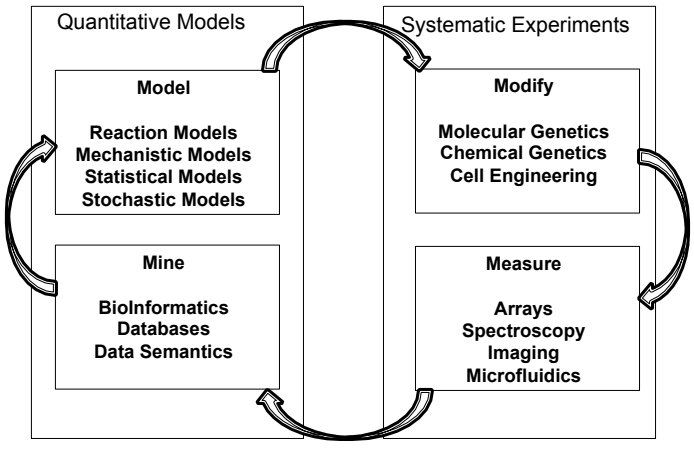
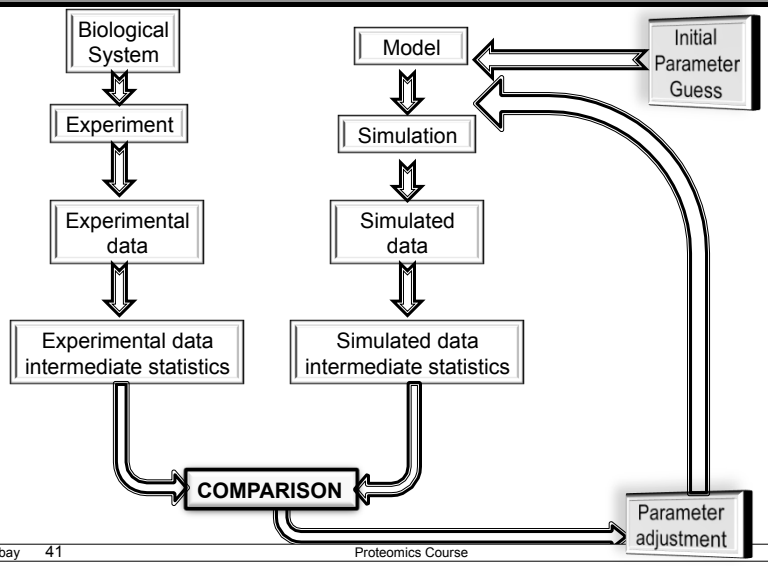
Frameworks for Modelling Schemes



Work-flow of Mathematical Modeling



Modelling of Probabilistic Processes



ODE and Stochiometric models

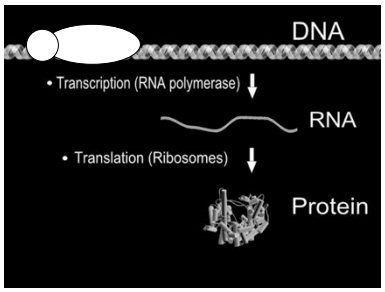
- Ordinary Differential Equations (ODE): mathematical relation that can be used for modeling biological systems
- Stochiometric model: modeling a biological network based on its stochiometric coefficients, reaction rates and metabolite concentrations

Systems approaches for studying biological networks: from post-transcriptional control to drug discovery

Dr. Sarath Chandra Janga

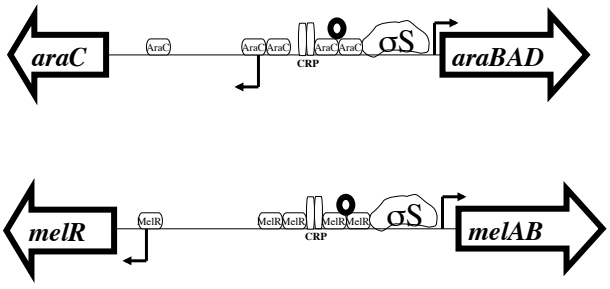
- Indiana University & Purdue University Indianapolis (IUPUI)

Central Dogma of Molecular Biology



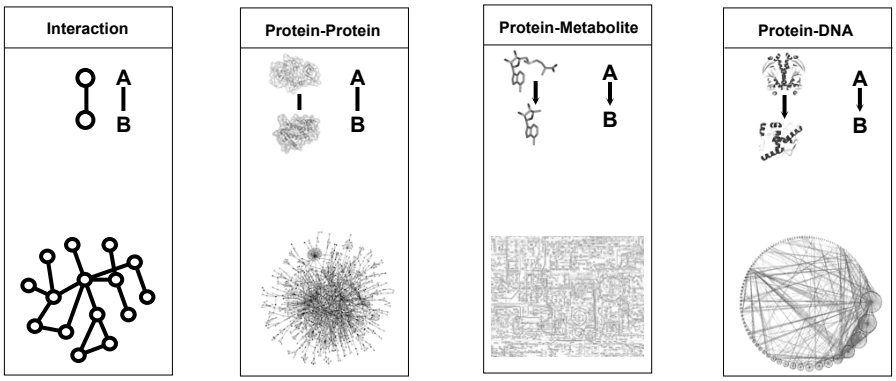
Transcription is regulated by a class of proteins called transcription factors that bind DNA and affect expression of the nearby genes

An example



Networks in Biology

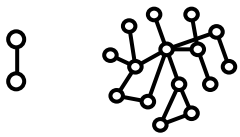
Network	Protein Interaction	Metabolic	Transcriptional
Nodes	*Proteins*	*Metabolites*	*Transcription factor Target genes*
Links	*Physical Interaction*	*Enzymatic conversion*	*Transcriptional Interaction*



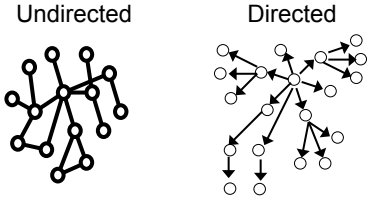
Graphs are objects, which are made of nodes and edges

Graph – a collection of nodes and links

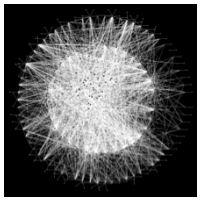
- **Nodes represent entities**
- **Links represent interactions between entities**

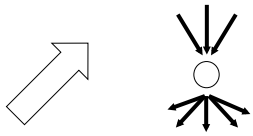


Graphs can be directed or undirected



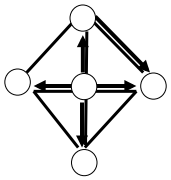
Graph Parameters





Degree
or connectivity

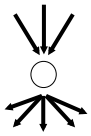
Path length



Clustering
coefficient

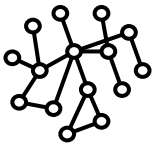
Degree of a node in a graph

Degree
or connectivity



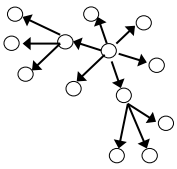
Degree of a node tells us
how many links the node
has to other nodes in a graph

Undirected



Degree = 2

Directed



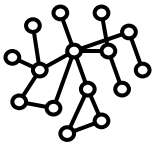
In-degree = 1
Out-degree = 3

Path length between two nodes in a graph

Path length

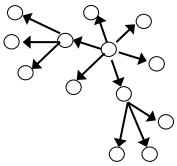
Path length is the shortest number of links needed to connect two nodes in a graph

Undirected



Path length = 1

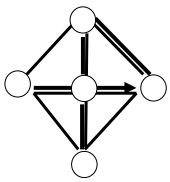
Directed



Path length = 2

Clustering coefficient of a node in a graph

Clustering coefficient

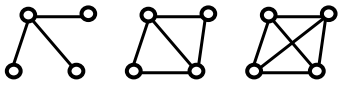


Clustering coefficient tells us how interconnected are the neighbors of a give node

$$CC = \frac{\text{\# links among neighbors}}{\text{\# all possible links among neighbors}}$$

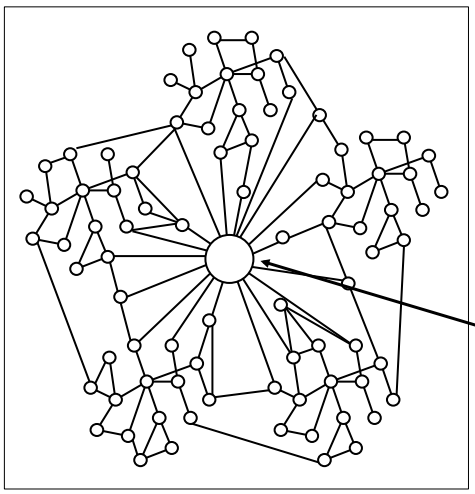
$$CC = \frac{2 \times M}{N \times (N - 1)}$$

N, neighbors of a node
M, links between neighbors of a node



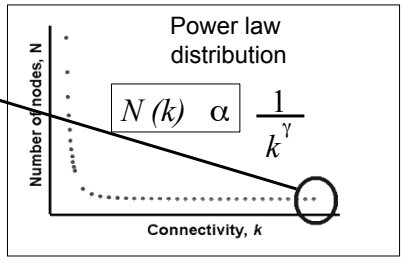
N=3, M=0 CC=0 | N=3, M=2 CC=0.66 | N=3, M=3 CC=1

Transcriptional networks are scale-free



Scale-free structure

Presence of few nodes with many links and many nodes with few links



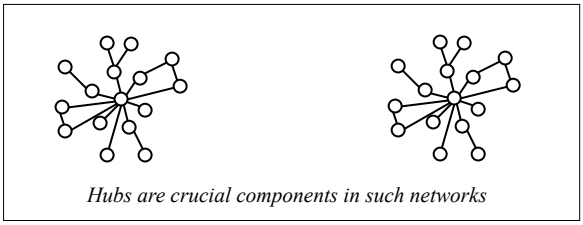
Scale free structure provides robustness to the system

Scale-free networks exhibit robustness

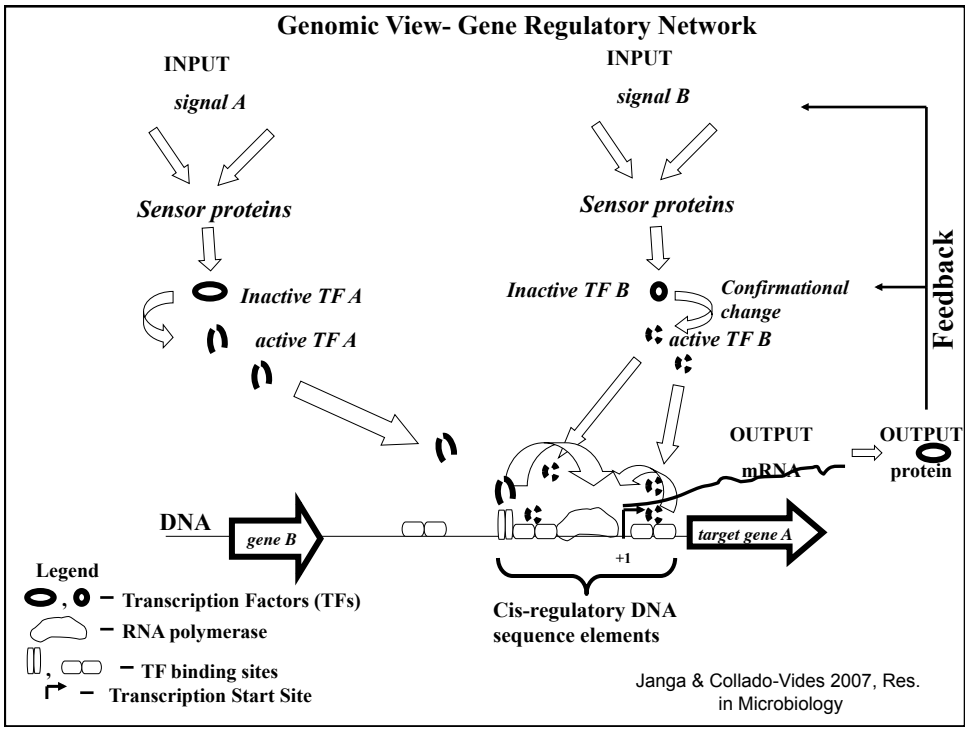
Robustness – The ability of complex systems to maintain their function even when the structure of the system changes significantly

Tolerant to random removal of nodes (mutations)

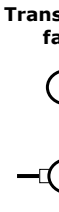
Vulnerable to targeted attack of hubs (mutations) – Drug targets

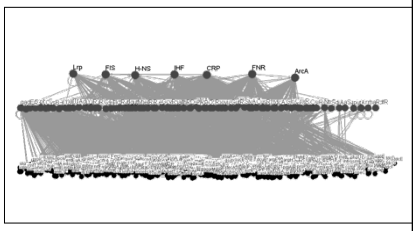


Hubs are crucial components in such networks



Structure of the transcriptional regulatory network





Basic unit
(Components)
transcriptional interaction

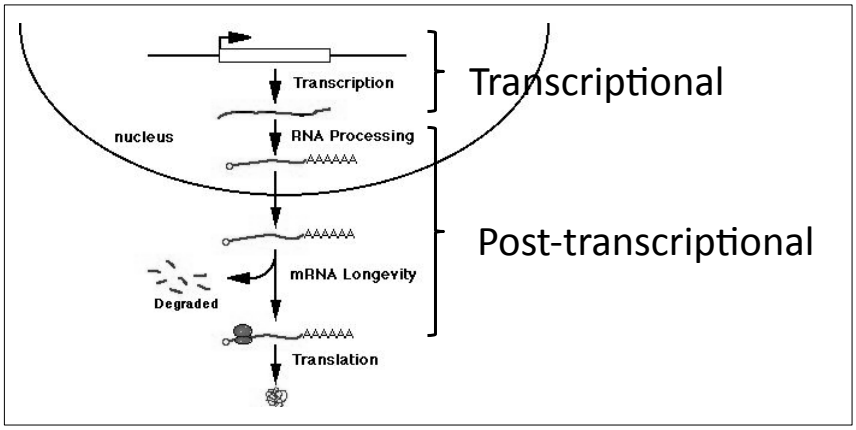
Motifs
(Local level)
patterns of Interconnections

Scale free hierarchical network
(Global level)
all transcriptional interactions in a cell

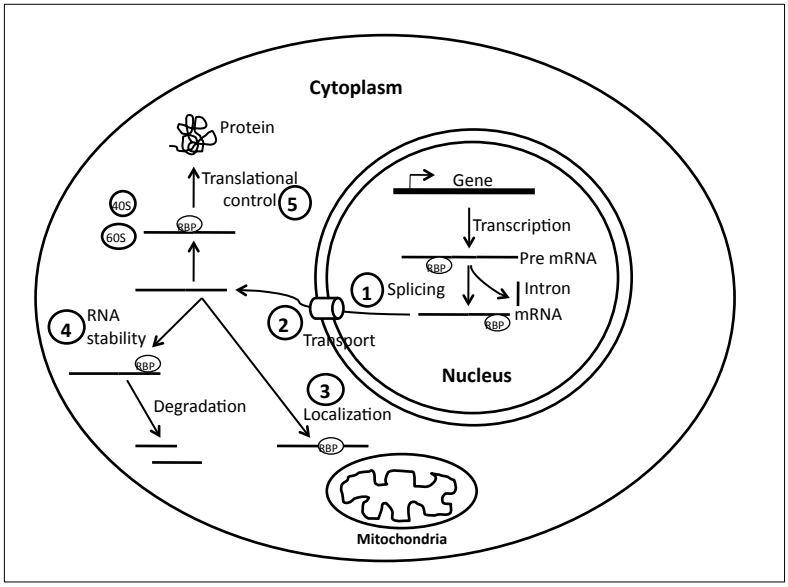
Janga & Collado-Vides 2007, Res. in Microbiology

Gene regulation beyond transcription

- **Gene regulation is a highly regulated and complex process**
- **Gene regulation takes place at several steps**

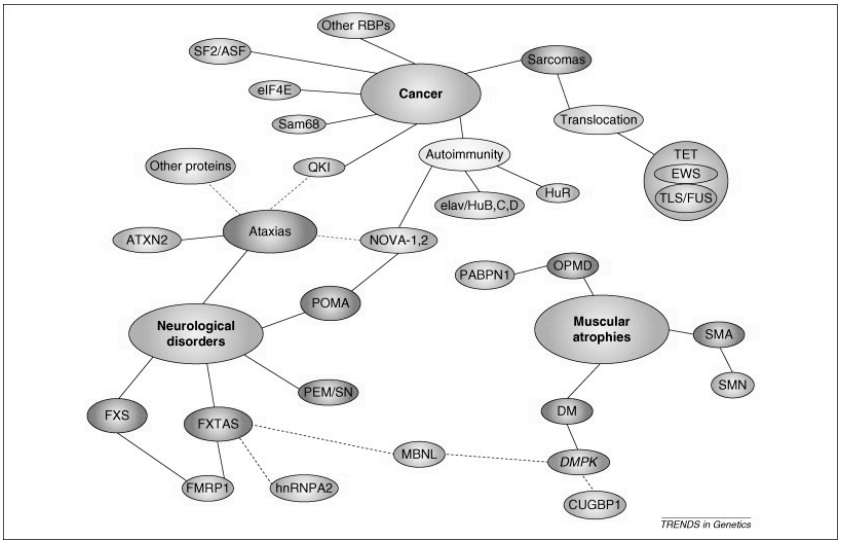


Diverse functions of RNA-Binding Proteins (RBPs)



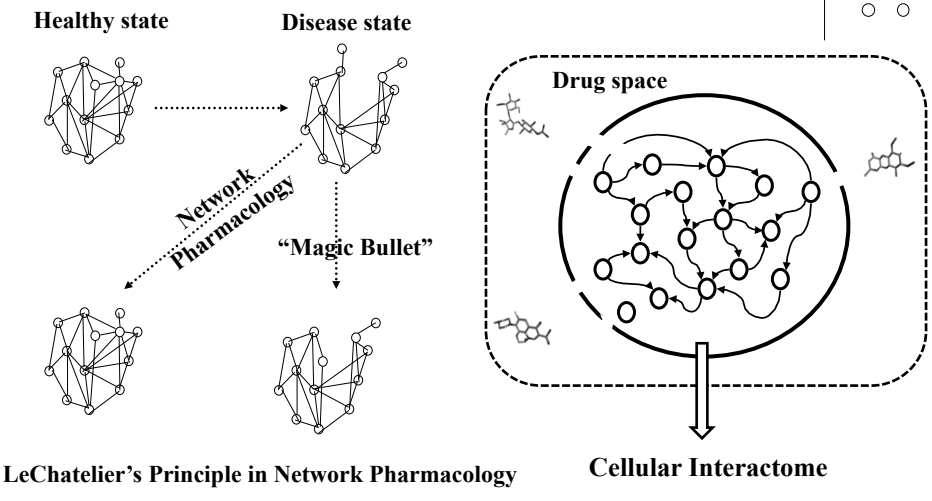
Mittal et al., 2009 PNAS

A network of RBPs in human diseases



Change in the expression dynamics of RBPs is associated with several diseases

Networks in drug discovery settings



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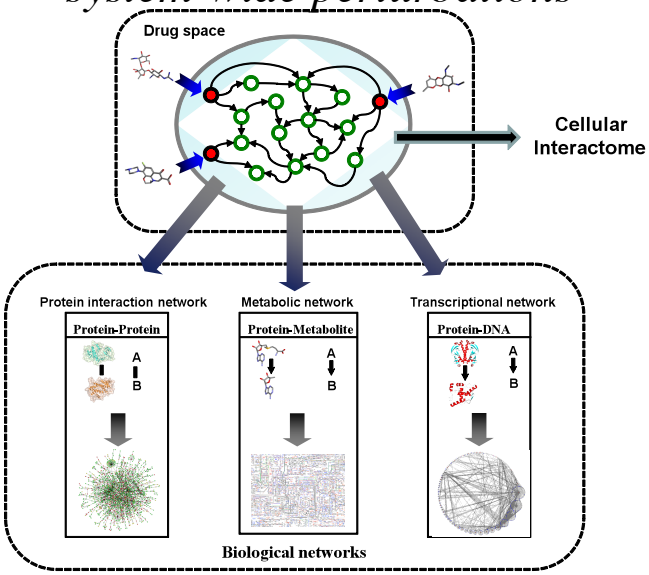
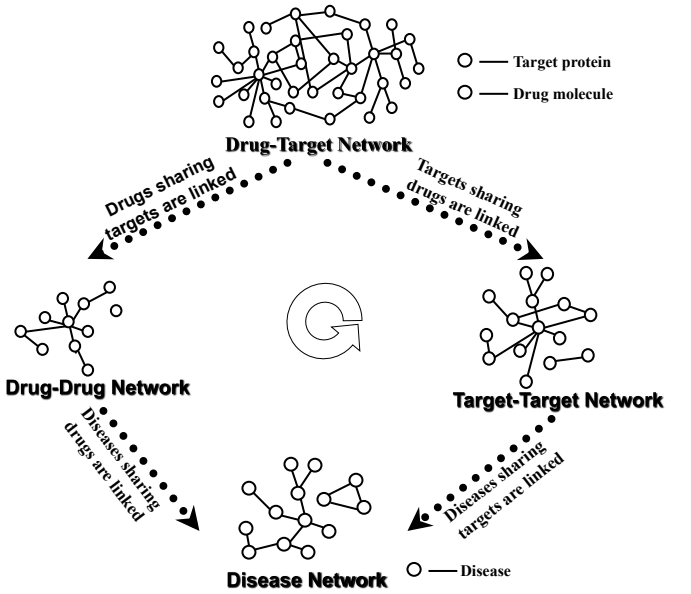
Integration of data for understanding system-wide perturbations



Janga SC. & Tzakos A. Molecular Biosystems 2009

What network pharmacology offers ?



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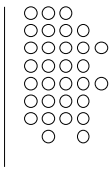
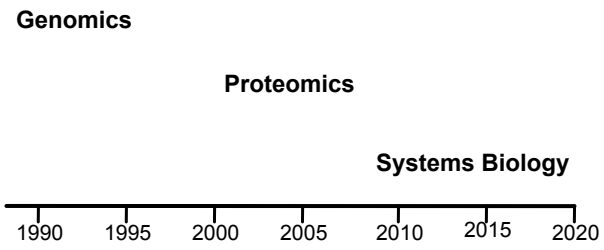
Conclusion



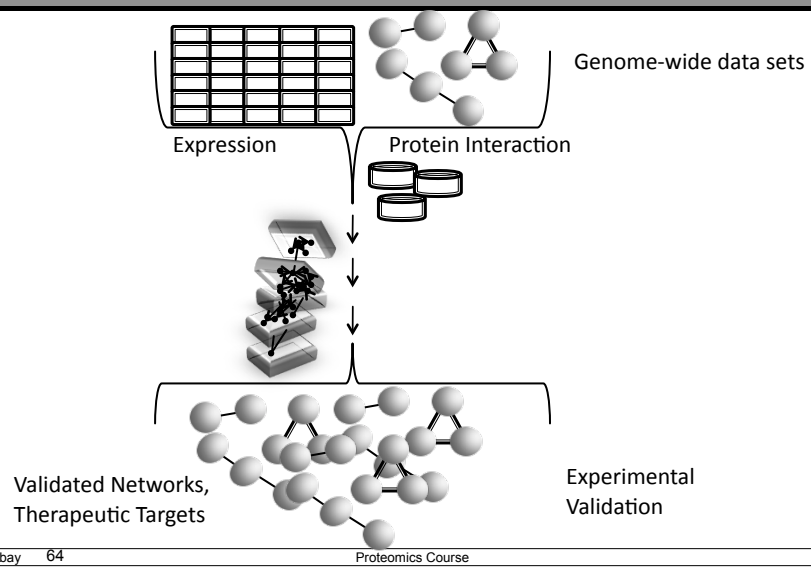
- Network-based approaches are essential for dissecting the design principles of biological systems
- They play an important role in biomarker identification and elucidation of key players responsible for the disease phenotype.
- Systems medicine can lead to the development of personalized medical treatment options in years to come with developments in high-throughput sequencing and other technologies.

"Omics" and Systems Biology

Omics and Systems Biology

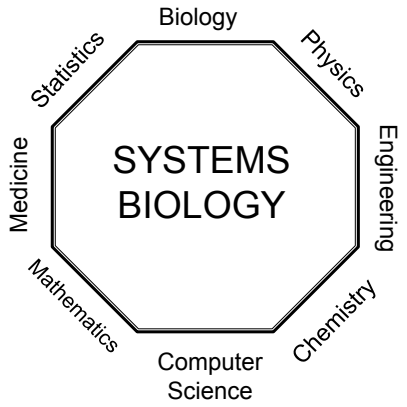


Systems study requires data-set from different approaches



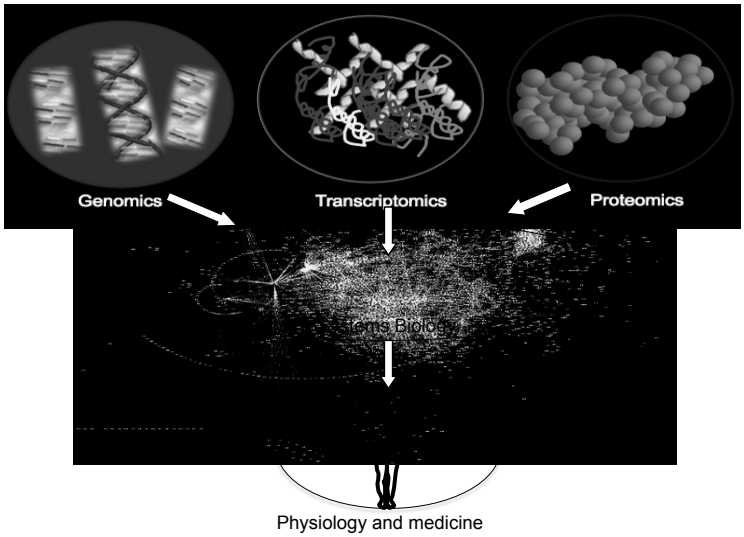
Systems study requires collaboration!

IPG strip



"Omics" to Physiology

IPG strip



Challenges: Systems Biology

- Systems biology is extremely challenging
- Understanding dynamics of biological networks requires modeling, simulation and understanding of biology
- Requires mathematical & statistical approaches

Proteomics and Systems Biology

- Proteomics is useful to understand complex signaling networks in biological systems
- Proteomics is indispensable for systems biology

Summary

- Proteomics
- Systems biology

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