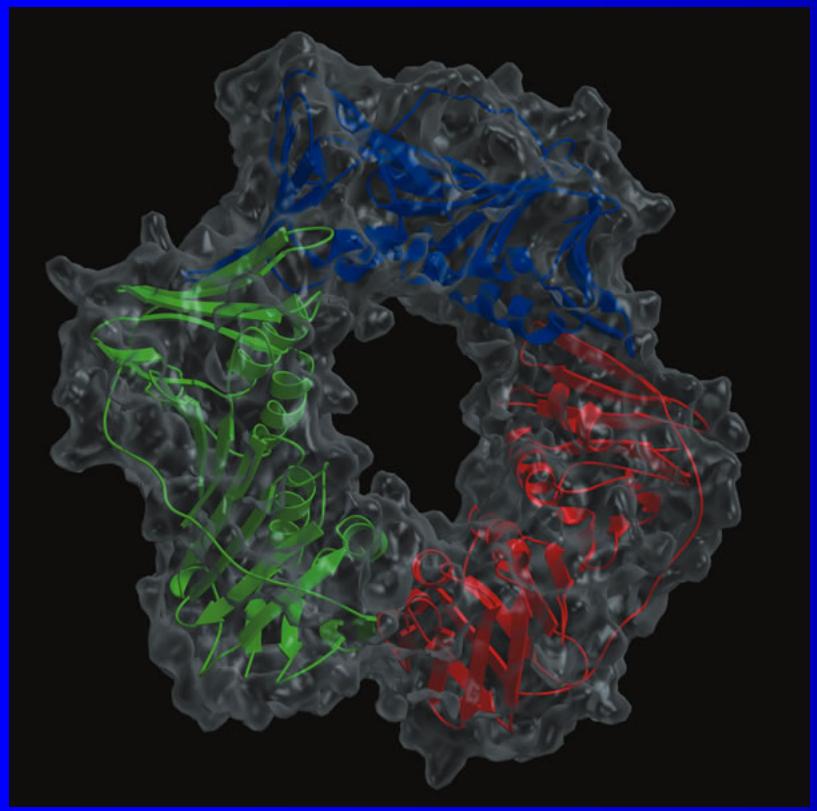
Creating In Silico Interactomes



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Objectives

- Define interactomes
  - Biological and in silico
- Describe the process of construction
- Relate the data structure
  - How this structure is comprehensive to detailing the data
  - Why this structure is good for some statistical modeling
- Simple examples in using the interactome
- Future Work

Introduction and Background

- Basic Terminology
  - Protein Complex
    - Group of 2 or more associated proteins
    - Conduct some biological process
  - Protein Complex Interactome
    - Coordinated set of protein complexes
    - Specific to each cell or tissue type
    - Variable over environmental conditions

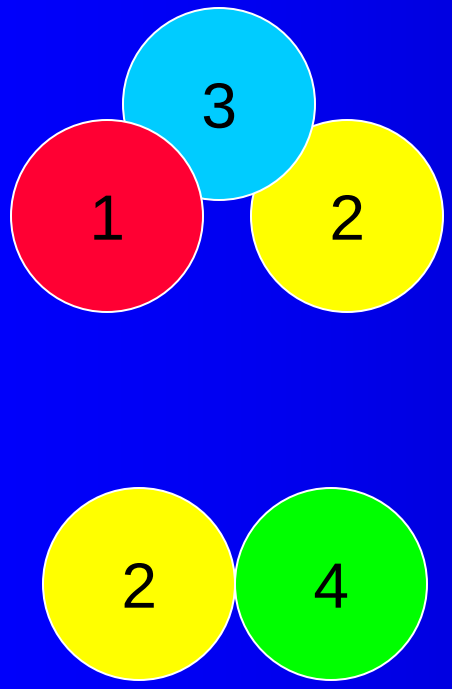
Graph Theoretic Representation

- Hyper-graph
  - Generalization of ordinary graph
    - Vertex set, V, is the collection of unique proteins
      - Let $|V| = n$
    - Hyper-edge, E, is the collection of unique protein complexes
      - Then $|E| \leq 2^n - (n+1)$
- Interactome $\leftrightarrow$ Hyper-graph
  - Most protein complex identification experiments occur in some biological interactome

In Silico Interactome

- Collection of estimated protein complexes representing an in silico model organism
  - The ISI is a simulated organism with which we can conduct computational experiments
- ISI is modeled after biological interactomes
- Storage of the ISI
  - Incidence Matrix Representation of the Hyper-Graph
    - Rows indexed by the vertices (expressed proteins)
    - Columns indexed by the hyper-edges (complexes)
    - Incidence is equivalent to membership

Interactome to Incidence Matrix



	*Complex*1	*Complex*2
Pr*otein*1	1	0
Pr*otein*2	1	1
Pr*otein*3	1	0
Pr*otein*4	0	1

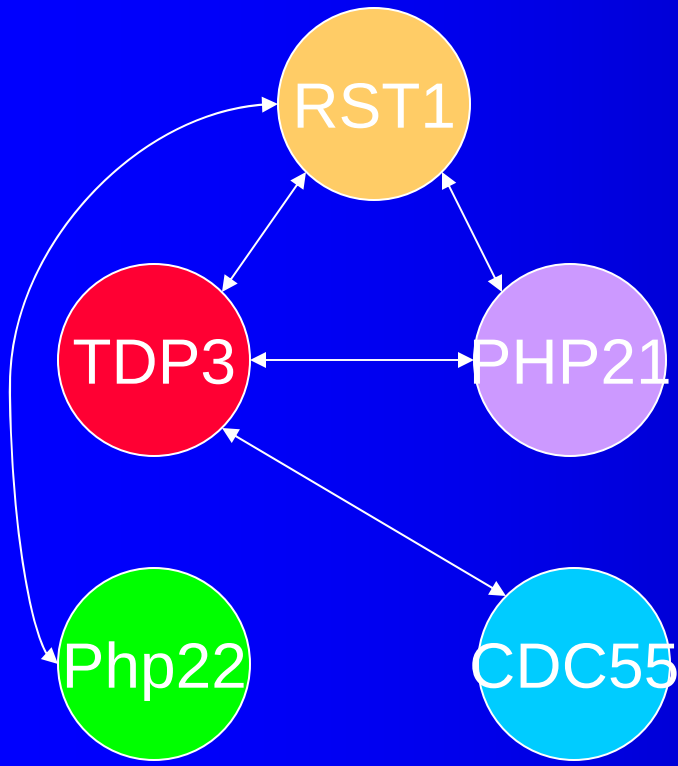
Why hyper-graph representation

The hyper-graph representation encapsulates more information than a graph representation.

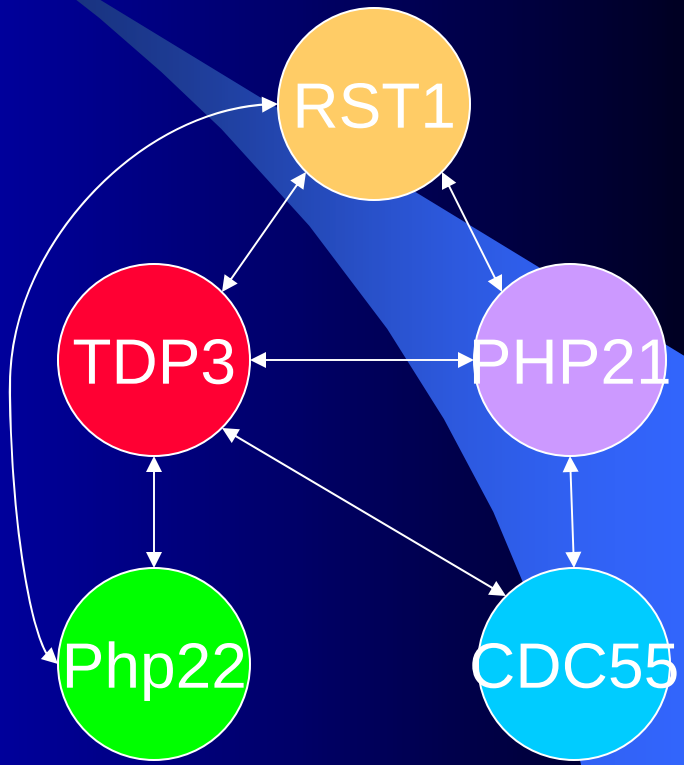
We look at the example of PP2A I, II, III

By example, we show why protein-protein interaction graphs and co-membership graphs cannot incorporate protein membership information

Protein-Protein
Direct Interaction
Graph

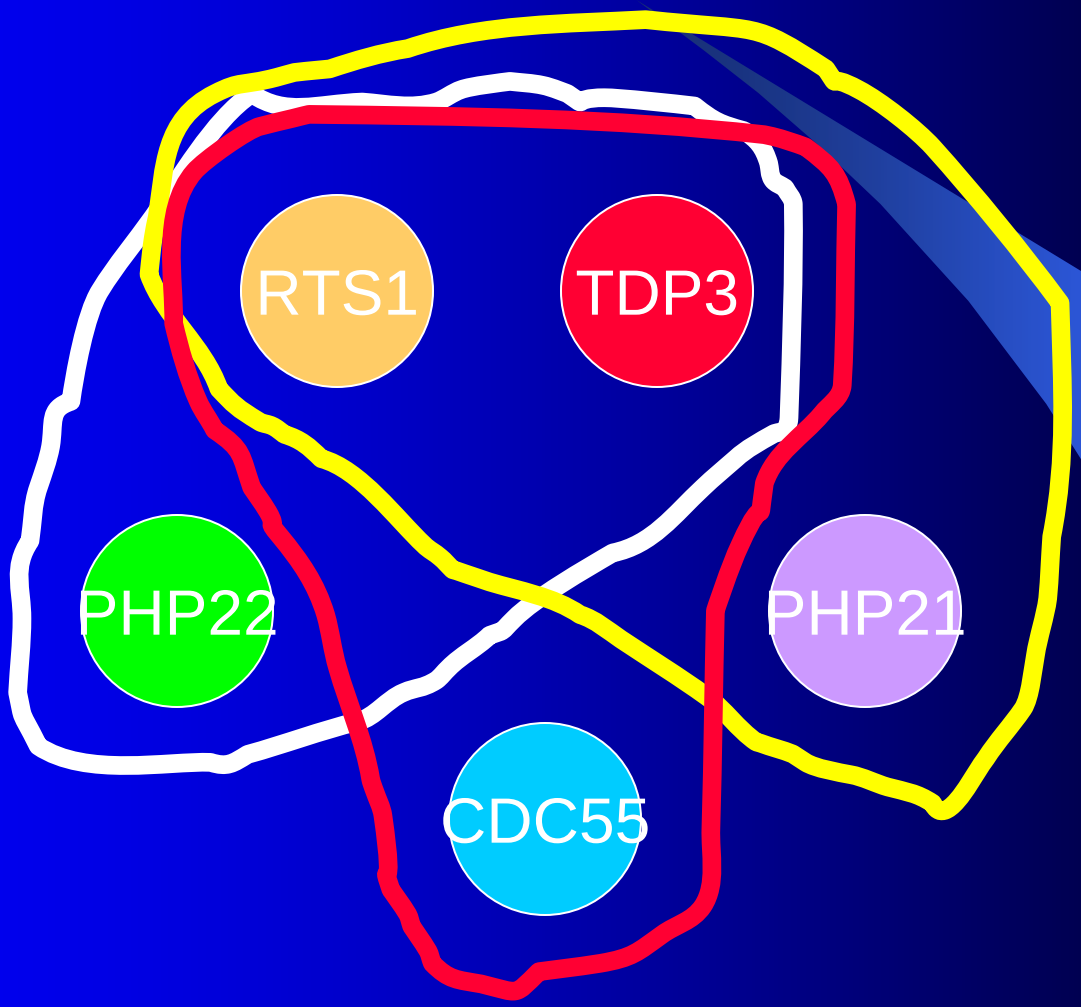


Protein- Protein Complex
Co-Membership Graph



Neither graph can determine Protein Complex Membership

A Hyper-Graph (Forgive me) details protein membership, co-membership, but not interaction data



Constructing the ISI

- Presently, the simulated model organism is based on Saccharomyces cerevisiae
- Constructing the in silico interactome
  - Collecting protein complex composition data
    - Gene Ontology
    - MIPS
    - High Through-Put Affinity Purification - Mass Spectrometric Experimentation
      - Protein Complex Estimation via apComplex

ISI - Limitations

- Comprehensive
  - It does not contain an exhaustive list of all protein complexes since it reflects known biology
- Definitive
  - It contains mostly estimated protein complexes via both low and high through-put technologies
- Meant to replace experimental de novo research
  - It cannot give insight to unknown biological complexes and interactomes

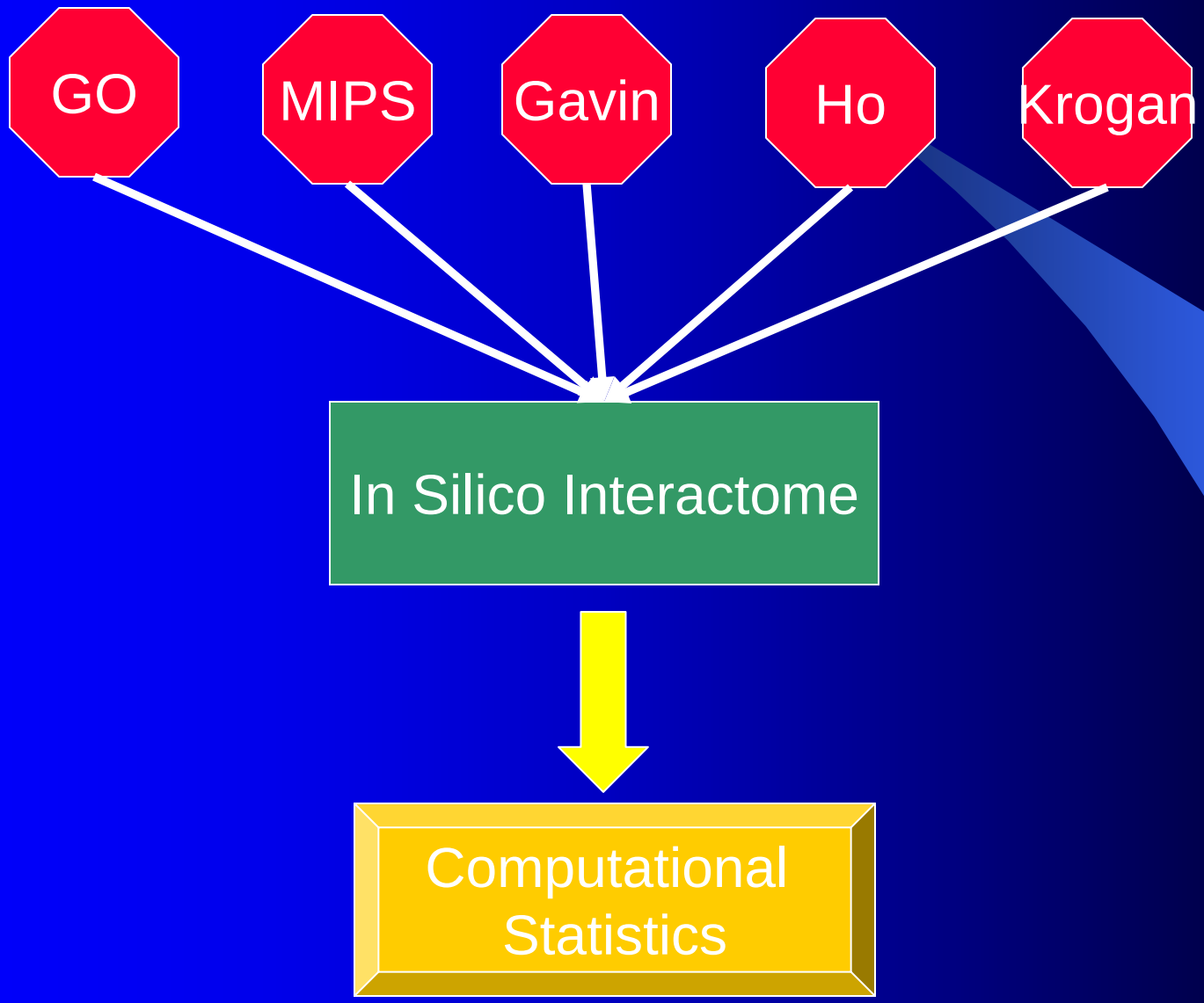
ISI - Benefits

- Dynamic
  - It can be updated and modified as new data is discovered and old data is revised
- Simplified
  - Redundancies from different data sources can be eliminated as well as irrelevant protein complexes
- Versatile
  - An ISI can be modeled after any organism from yeast to mice to men

Why build in silico interactomes

- Reasons to build valid in silico interactomes:
  - Provides one single data structure with which to conduct in silico experiments
  - Provides tool with which simulated wet-lab experiments can be conducted
  - Use in the generation of multiple data sets
  - Develop tools and strategy for small scale experiments
  - Study of perturbation in networks
  - Effects of varying sampling paradigms on large, non-random networks

Integrating Data and Deriving Statistics



In Silico Interactome for Yeast - ScISI

- Computational parsing data from GO and MIPS
  - Term mining
    - [Cc]omplex
    - Suffix “-ase” (e.g. RNA polymerase II)
    - Suffix “-some” (e.g. ribosome)
- Manual parsing resultant protein complexes
- Collecting estimates from apComplex
  - Experiments
    - Gavin et al. (2002, 2006*)
    - Ho et al. (2002)
    - Krogan et al. (2004)

ScISI - a model example

- In silico S. cerevisiae
  - 1661 unique expressed proteins
  - 734 distinct protein complexes
- Basic statistical profile
  - Complex
    - Cardinality range = [2,57]
    - Median cardinality = 4
    - Mean cardinality = 5.98
  - Protein
    - Membership range = [1,31]
    - Median membership = 1
    - Mean membership = 2.64

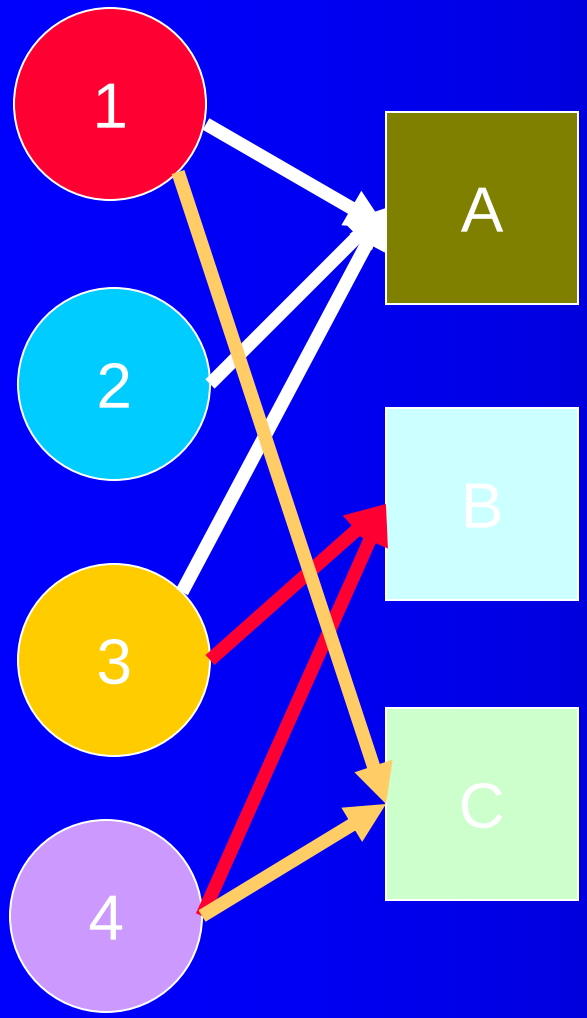
In Silico experiments on ScISI

- Determining protein complex structures
  - Let A be the incidence matrix of ScISI
    - Then $[AA^T]_{ij}$ counts the number of complexes to which protein i and protein j belong, that is how many complexes these two proteins share co-membership
  - Transformation gives a measure of protein affiliation but not direct binary interaction

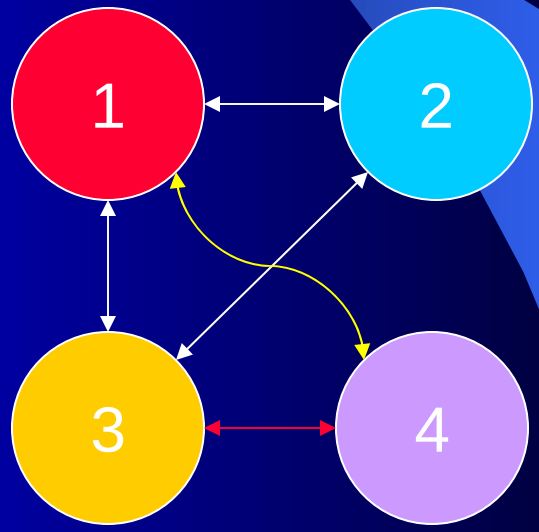
Graphical representation of in silico experiments

- We make use of the equivalence of hyper-graphs to bi-partite graph
  - Equivalence is determined by letting the set of hyper-edges be the second set of nodes.
- The operation AA^T is a contraction on the protein complex nodes of the bi-partite graph
  - This process takes us from protein complex membership to protein-protein complex co-membership

Bi-partite Graph: Protein Complex Membership



Ordinary Graph: Protein-Protein Complex Co - Membership



Where to from here?

- Let's re-iterate the 5 reasons to build valid in silico interactomes:
  - Provides tool with which simulated wet-lab experiments can be conducted
  - Use in the generation of multiple data sets
  - Develop tools and strategy for small scale experiments
  - Study of perturbation in networks
  - Effects of varying sampling paradigms on large, non-random networks
- All 5 of which are still open ended…

Future Direction

- An interesting question…
  - Many of the protein complexes are estimates obtained from Affinity Purification - Mass Spectrometry experiments
  - Can we validate these estimates?
    - Each interactome built needs to be validated before conducting computational experiments
  - We present two different methods to validate the interactomes.

Validating ISI

- Using direct binary interaction data to verify protein complex composition
  - Necessary and sufficient condition is that induced interaction graph be connected on the sub-set of proteins in each protein complex
- Hard to verify
  - Binary interaction data is sparse
  - Error Rates are extremely high
  - There is a need to decipher between true negative interactions between two proteins and un-tested interactions between two proteins
  - Induced interaction graph is almost always dis-connected

Validating ISI

- Simulation Models
  - Simulate the AP-MS technology and derive data-sets on which we can apply estimation algorithm.
  - Determine how effective estimation algorithm based on statistical significance
  - Compare with other estimation algorithms