Types of biological networks

I. Intra-cellurar networks

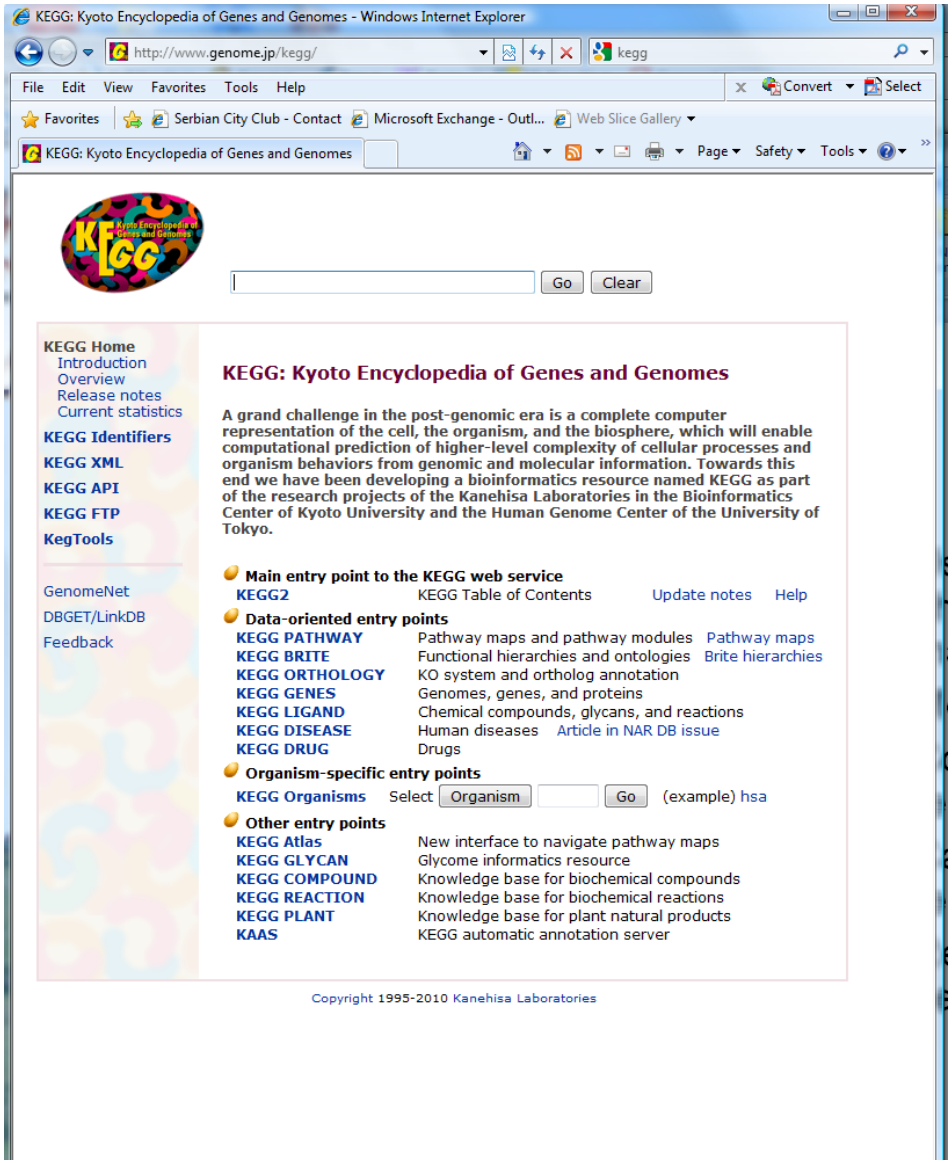
Some intra-cellular networks:

1. Metabolic networks
2. Transcriptional regulation networks
3. Cell signalling networks
4. Protein-protein interaction networks
5. ...

Metabolic networks

- A network of biochemical reactions in a cell
- Partially experimental, partially reconstructed from genome sequence – see the WIT paper from *Nucleic Acids Research*, 2000
- Available for many organisms, from bacteria to human
- Available on-line:
  - KEGG (Kyoto Encyclopedia of Genes and Genomes) – info on genes, proteins, reactions, pathways for eukaryotes and prokaryotes
  - GeneDB – contains similar info
  - BioCyc, EchoCyc, MetaCyc – more specialized info on particular species
  - WIT, renamed to ERGO

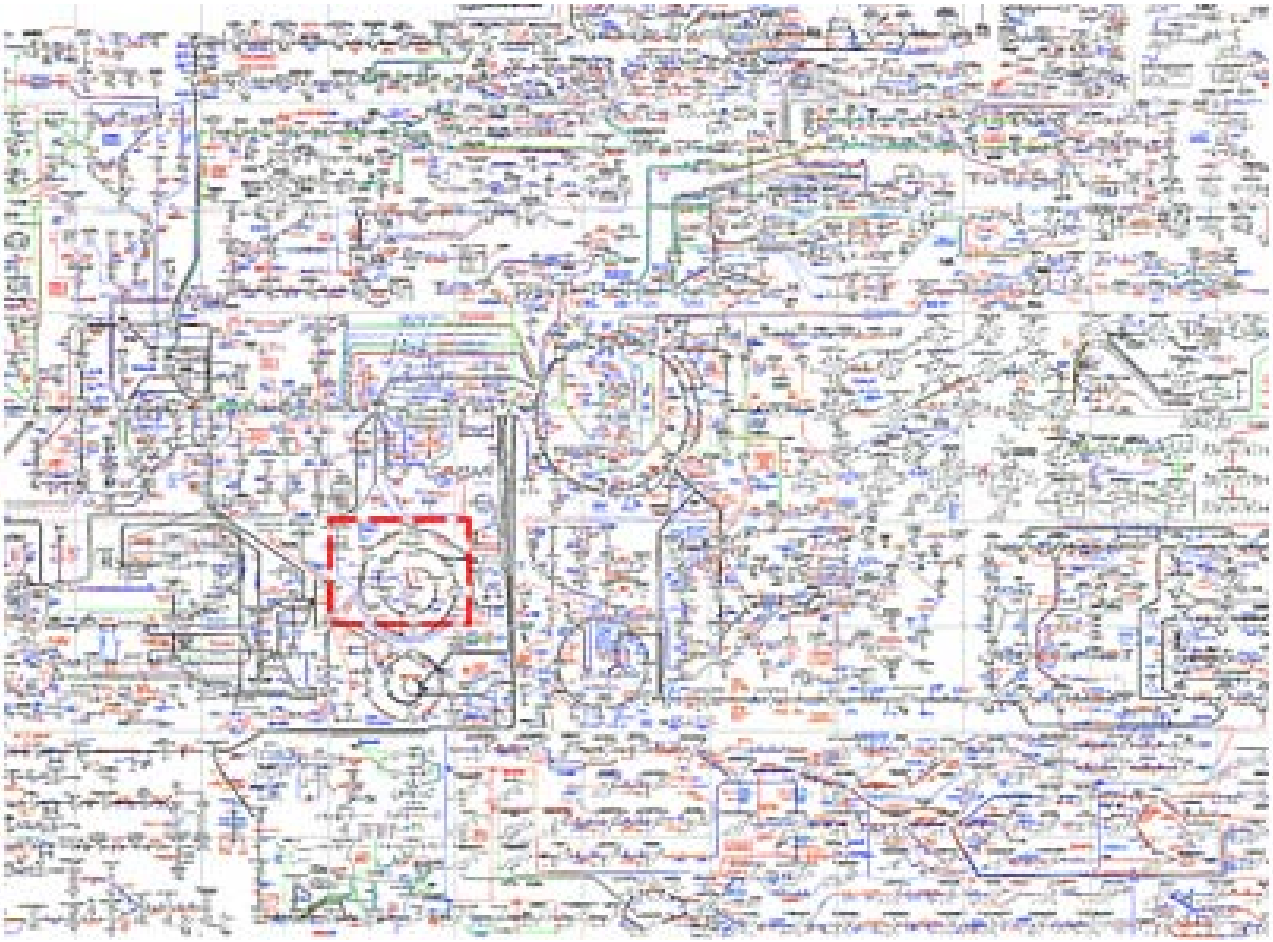
Metabolic networks



Metabolic networks

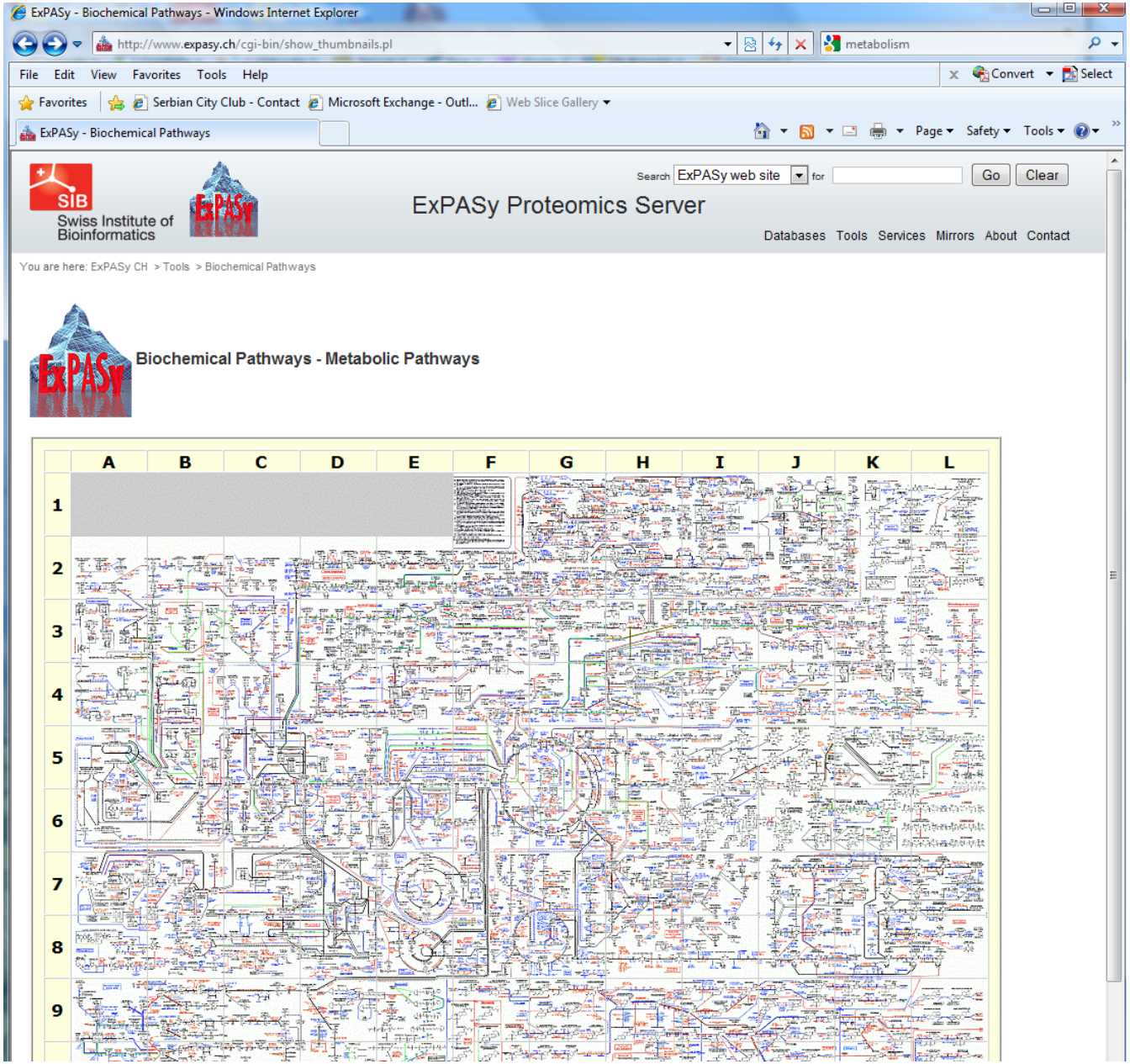
- Used for studying and modeling *metabolism:*
  - a set of chemical reactions that happen in living organisms that allows an organism to:
    - respond to the environment,
    - grow,
    - reproduce,
    - maintain its structure
- Modeling from *network topology* (topic of this class) to predictive toxicology
- Consist of *metabolic pathways:*
  - Series of chemical reactions occurring within a cell,
  - Catalyzed by *enzymes* -- proteins that regulate chemical reactions
  - Results in a *metabolic product* to be used/stored in the cell, or
  - Initiation of another metabolic pathways (called *flux generating* step)

Metabolic networks



Example from *Viz4All*, University of Maryland, College Park:
http://www.cs.umd.edu/class/spring2006/cmsc838s/viz4all/v4a_vis.html

Metabolic networks



Metabolic networks

Biochemical Pathways - Map No. J6 - Windows Internet Explorer

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Biochemical Pathways - Map No. J6

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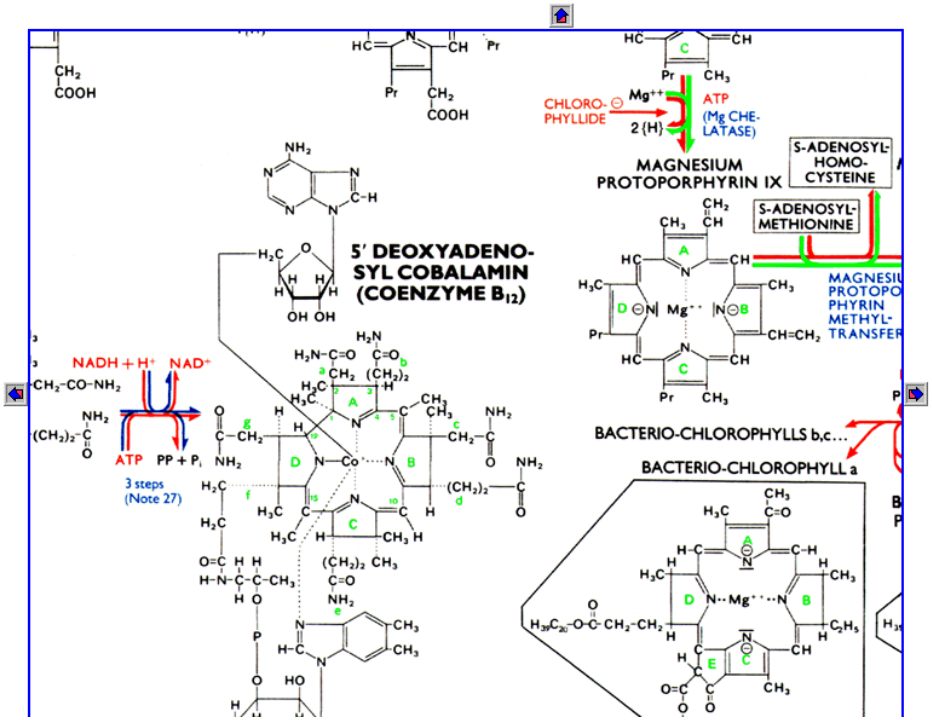
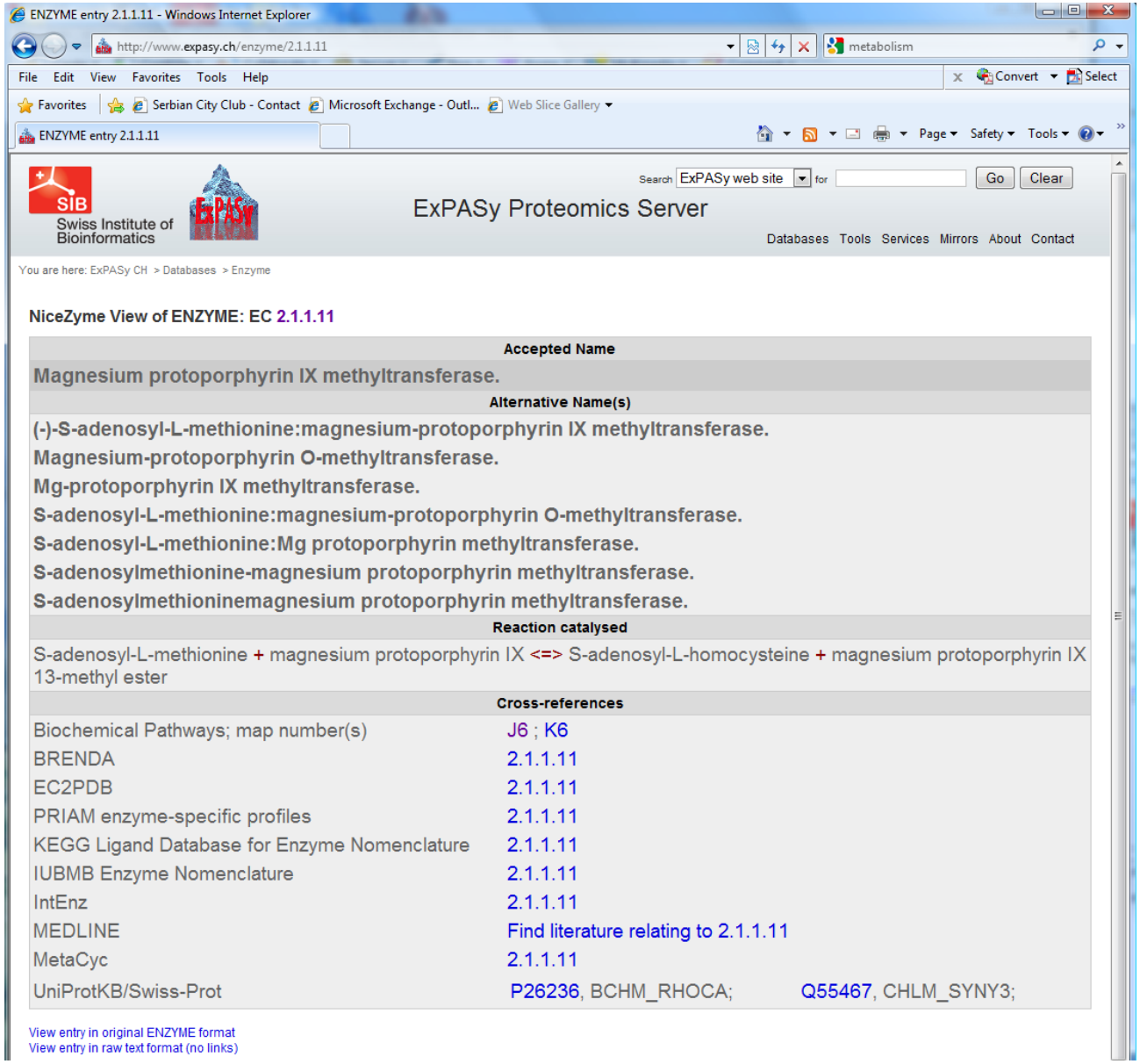
Biochemical Pathways Map No. J6

This is field J6 of the Roche Applied Science "Biochemical Pathways" wall chart. If you would like to look at one of the adjoining fields of the map, you can click on the corresponding arrow icon. Then both the current map **and** the requested adjoining map will be displayed, and again you will have the possibility to "navigate" through the whole map.

You can also click on one of the enzyme names (printed in blue) appearing in the map, and you will obtain the corresponding entry of the ENZYME Data Bank.



Metabolic networks



Metabolic networks

- Metabolic pathways of a cell form a *metabolic network*
- Metabolic pathways include the main chemical, mostly enzyme-dependant reactions needed to keep an organism in *homeostasis,* which is an internal regulation that maintains a stable, constant condition of a living system
- Directed edges are drawn between *enzymes* (proteins that catalyze (accelerate) chemical reactions) and *substrates* (molecules acted upon by an enzyme)
- Thus, enzymes and substrates correspond to *nodes*, *directed edges* to metabolic reactions in a metabolic network.

Metabolic networks

Further readings:

- H. Jeong, B. Tombor, R. Albert, Z. N. Oltvai & A.-L. Barabási, “The large-scale organization of metabolic networks,” *Nature* 407, 2000.

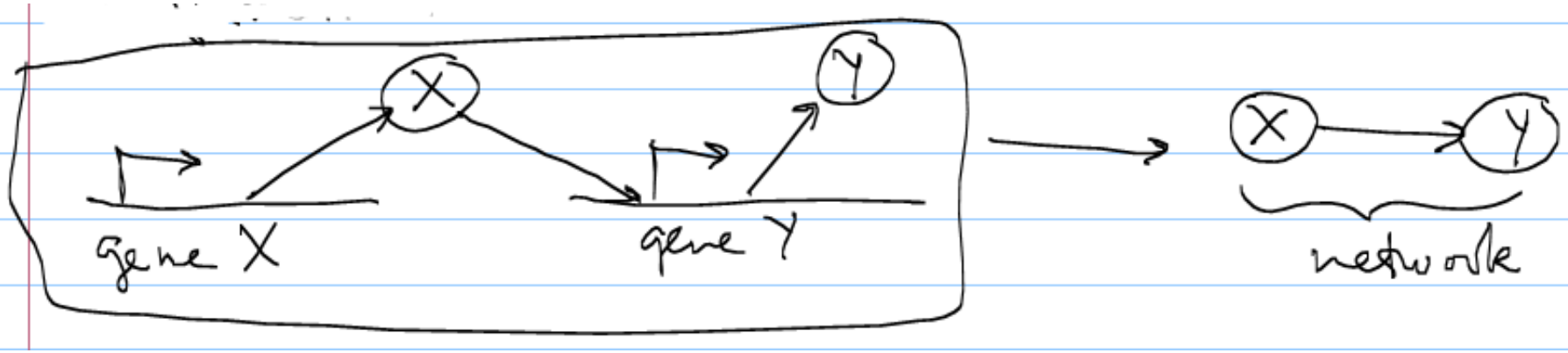
- R. Tanaka, “Scale-rich metabolic networks,” *Physical Review Letters* 94, 2005.

Transcriptional regulation networks

- Model regulation of *gene expression* (gene regulation)
- *Gene regulation* is a process by which information from genes is turned into *gene products* (*RNA* or *protein*)
- Gene regulation gives a cell control over its structure and function, e.g.:
  - *Cellular differentiation* (a process by which a cell turns into a more specialized cell type)
  - *Morphogenesis* (a process by which an organism develops its shape)
  - Adaptability...

Transcriptional regulation networks

- Genes are the nodes and the edges are directed:



- *Transcription factor* protein X, binds regulatory DNA regions of a gene to *regulate* (stimulate or repress transcription of a gene) the production rate of protein Y

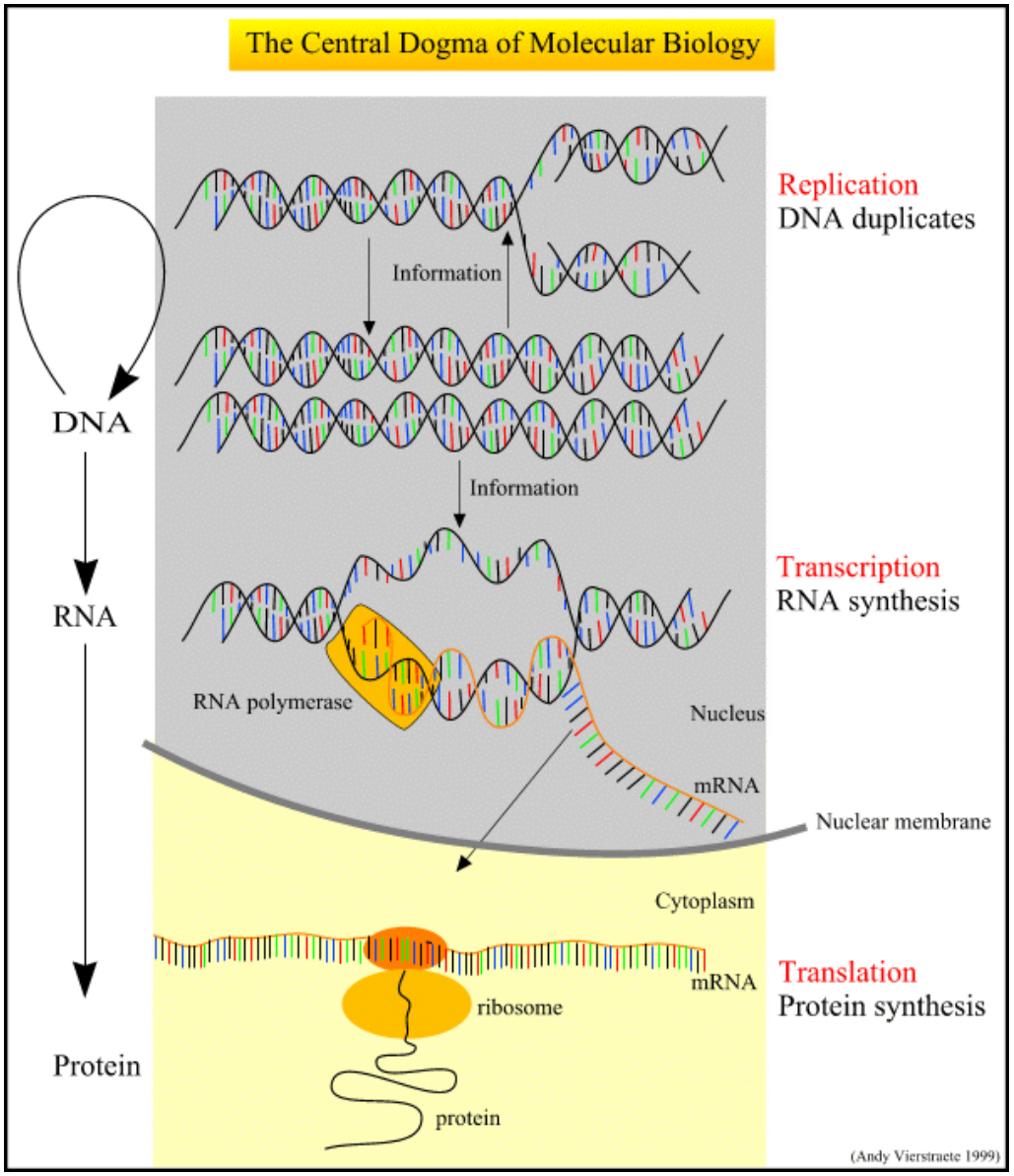
Transcriptional regulation networks

Problem: Stimulation and repression of gene *transcription* are both represented the same way in the network.

Available for *model organisms* = non-human species manipulated and studied to get insights into workings of other organisms:

- *Saccharomyces cerevisiae* - baker's yeast (see Milo *et al.,* 2002 from the class readings)
- *Escherichia coli* (see Shen-Orr *et al., 2002)*
- Sea urchin (see Davidson *et al.,* 2002)
- Fruitfly *D. melanogaster*

The Central Dogma of Molecular Biology

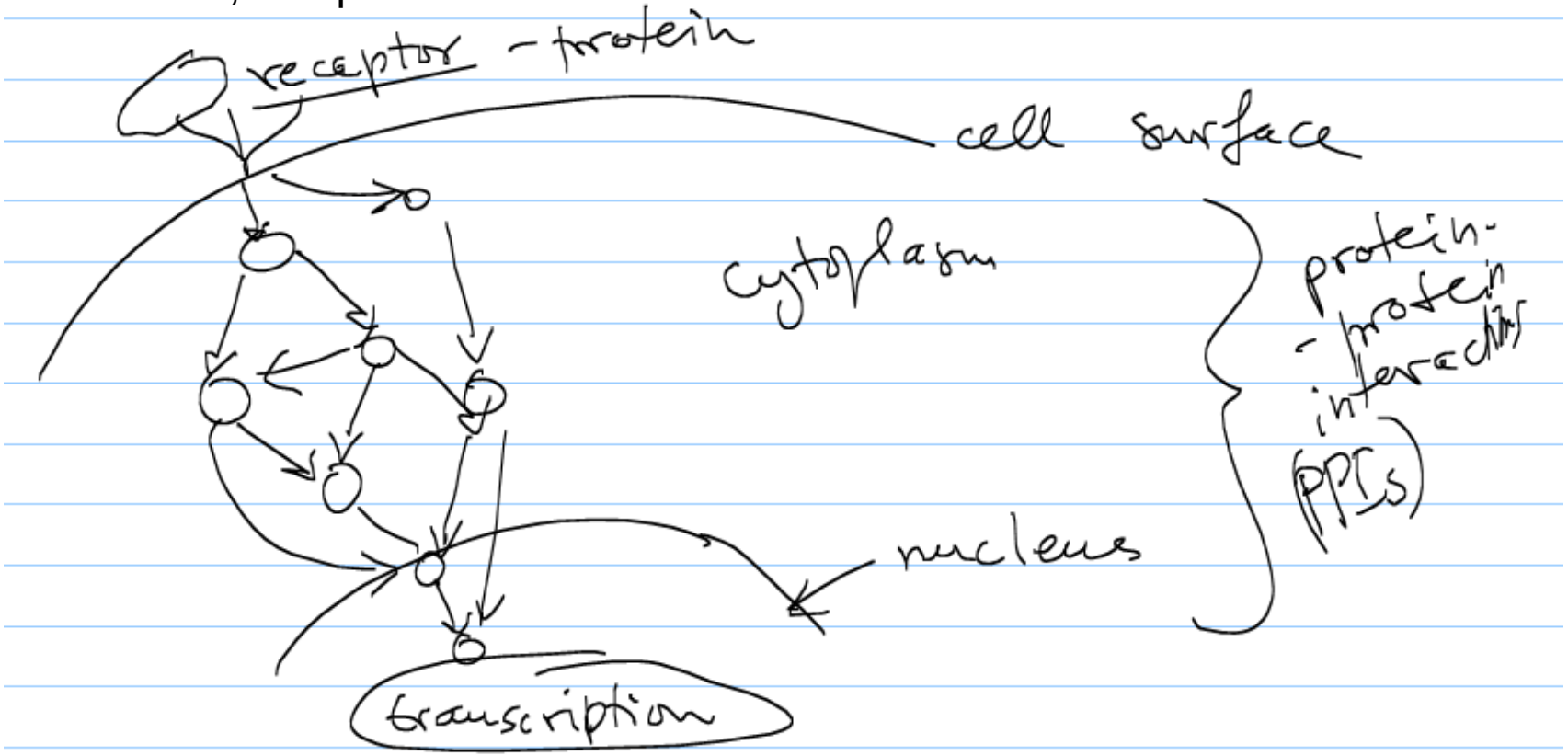


Cell signaling networks

- *Cell signaling* is a complex system of communication that governs basic cellular activities and actions, e.g., development, repair, immunity etc.
- The cell converts one kind of signal to another
- Errors in signaling cause serious diseases, e.g., cancer, autoimmune diseases, diabetes etc.
- These networks consist of *signaling pathways:*
  - Ordered sequences of biochemical reactions in a cell
  - Changes induced by *receptor* (protein that receives and responds to a stimulus) activation
- In these networks, proteins are the *nodes* and the *edges* between them are *directed*
- In this course – *systems biology* view of signaling

Cell signaling networks

Schematic, complex otherwise:



The entire set of changes induced by receptor activation is called a *signal transduction pathway* / *signaling pathway*

Cell signaling networks

Famous examples (lots of literature on them):

1. *Mitogen-activated protein kinase (MAPK)* pathway (originally called “ERK” pathway)
   - MAPK protein is an enzyme, a *protein kinase,* which can attach *phosphate groups* to target protein,

     (such as to a *transcription factor*)

     E.g.:
     - MYC is an *oncogene* transcription factor (oncogene is a gene which when mutated or expressed at high levels helps turn a normal into a tumor cell) expressed in a wide range of human cancers
       - MAPK can *phosphorilate* (attach phosphate group) MYC and so alter gene transcription and cell cycle progression
     - EGFR = “epidermal growth factor receptor”
       - activates MAPK pathway
       - mutations affecting its expression/activity can result in cancer

Cell signaling networks

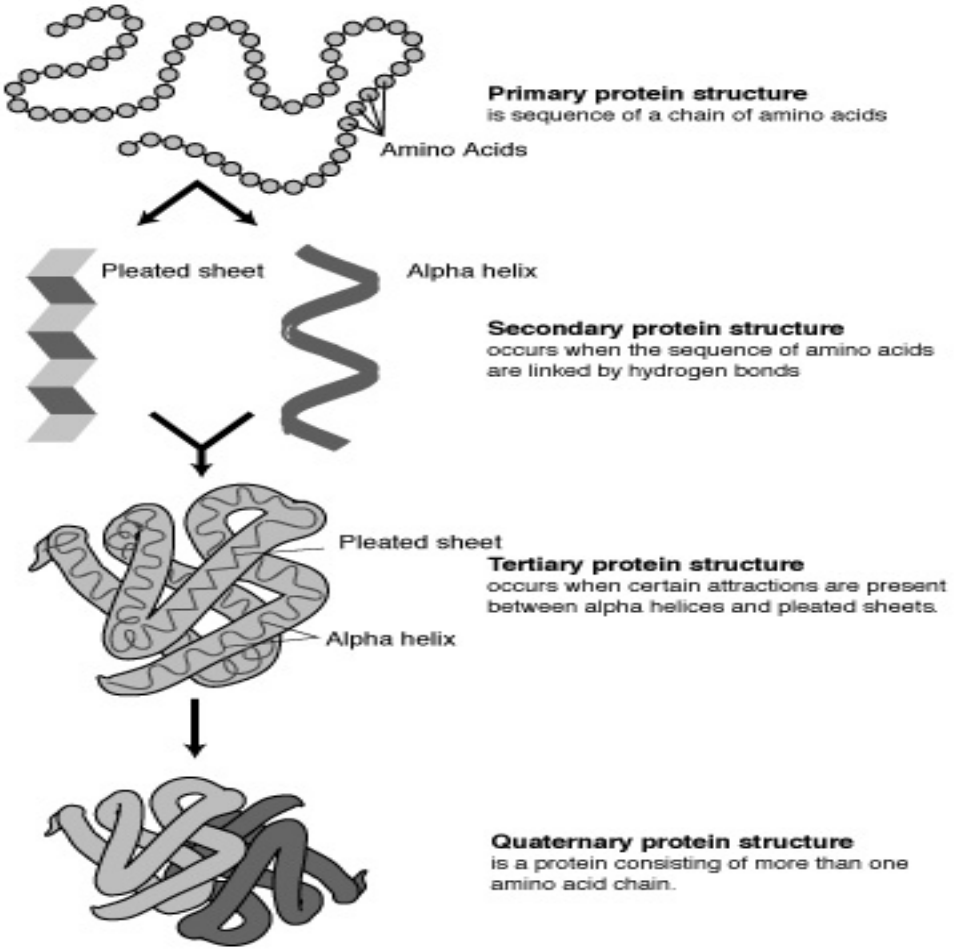
2. *Hedgehog signaling pathway*
   - One of the key regulators of animal development
   - Conserved from fly to human
   - Establishes basis of fly body plan
   - Important during *embryogenesis* (the process by which the embryo develops) and *metamorphosis* (from larva to pupa to adult)

3. *TGF-beta signaling pathway*
   - The “transforming growth factor” (TGF) signaling pathway
   - Involved in:
     - cell growth,
     - cell differentiation
     - *apoptosis* (programmed cell death)

Protein-protein interaction networks

- A *protein-protein interaction (PPI)* usually refers to a physical interaction, i.e., binding between proteins

Protein structure:



Protein-protein interaction networks

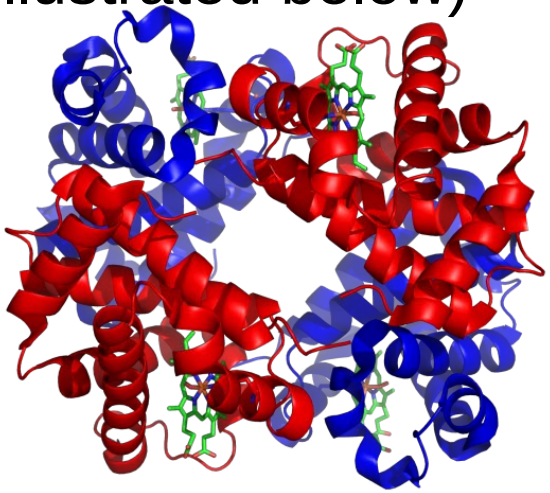
- Can be other associations of proteins such as functional interactions – e.g., synthetic lethality (see next class)
- PPIs are very important for structure and function of a cell:

  - participate in signal induction

    → play a role in many diseases (e.g., cancer)

  - can be *stable interactions* to form a *protein complex*

    (a form of a quaternary protein structure, set of proteins which bind to do a particular function, e.g., ribosome, hemoglobin – illustrated below)



Protein-protein interaction networks

- can be *transient interactions*, brief interactions that modify a protein that can further change PPIs
  - e.g., protein kineases, add a phosphate group to a target protein.
  - A protein can carry another protein (e.g., *nuclear pore importins* – proteins that carry other proteins from cytoplasm to nucleus and vice versa)
- Transient interaction form the *dynamic part of PPI networks*
- Some estimates state that about 70% of interactions is stable and 30% are dynamic

Protein-protein interaction networks

PPI are essential to almost every process in a cell.

Thus, understanding PPIs is crucial for understanding life, disease, development of new drugs (most drugs affect protein-protein interactions).

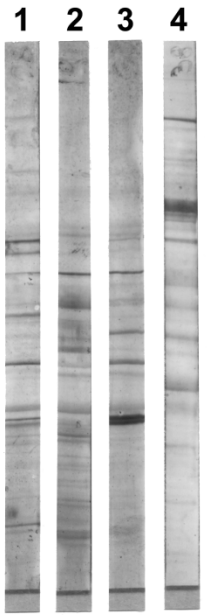
Methods to detect PPIs

- Biological and computational approaches.
- None are perfect, i.e., high rates of *false positives* (interactions present in the data sets that are not present in reality) and *false negatives* (missing interactions)

Protein-protein interaction networks

Methods to detect PPIs (continued):

1. Co-immunoprecipitation (CoIP, “Pull-down”):
   - The protein of interest is isolated with an antibody specific to the protein.
   - Interacting partners (proteins) of the protein, that stick to the protein of interest, are then identified by:
     - *gel electrophoresis techniques*, which separate proteins by mass, e.g.,
       - Western blotting
       - Mass spectrometry (see below)
     - They identify constituents of a protein complex
   - Verifies interactions between suspected interacting partners
   - Not a screening approach



Protein-protein interaction networks

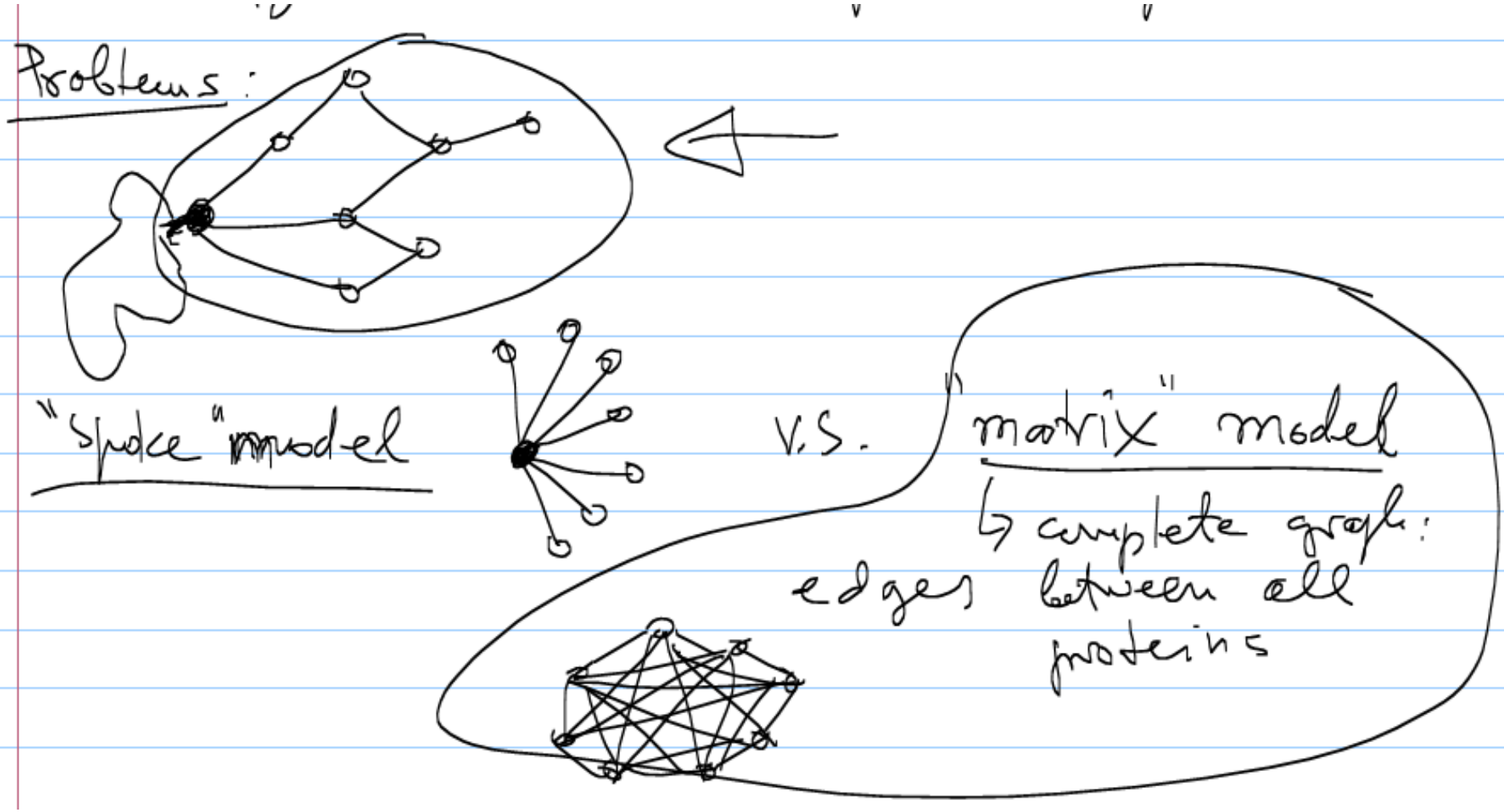
Methods to detect PPIs (continued):

- Problems:
  - "spoke" model (bipartite graph $K_{1,n}$) versus
  - "matrix" model (complete graph, K_n)

  of PPIs in a protein complex?

  Schematic:

Protein-protein interaction networks



Protein-protein interaction networks

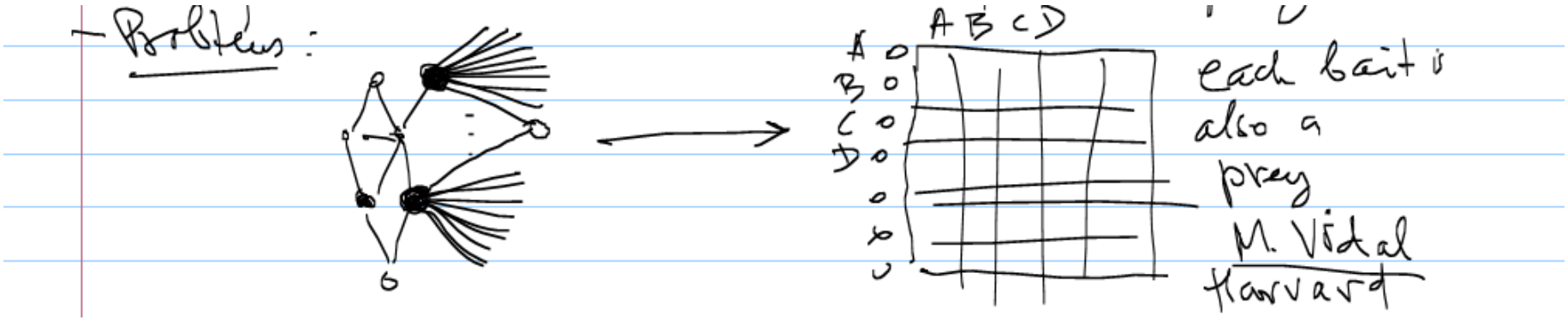
Methods to detect PPIs (continued):

2. Yeast Two-hybrid screening (Y2H)

- Investigates interaction between *artificial* (genetically engineered) *fusion proteins* (creted from two or more proteins or peptided), one to a *reporter gene* (a gene attached to another gene) and the other to a *transcription factor*.
- If the interaction exists, a reporter gene is transcriptionally activated.
- It happens in yeast nucleus.
- One protein (in PPI) is “bait”, the other is “prey”

Protein-protein interaction networks

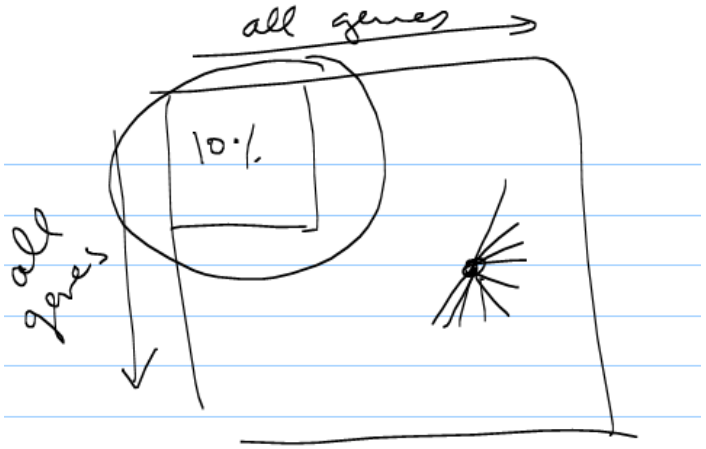
- Potential problem:
  - Interest in a particular pathway of, say 15 proteins
  - These 15 proteins are all “bates”
  - There is an order of magnitude more “prays”
  - This imposes a particular structure on the PPI network by experimental design without reflecting the underlying network topology



Thus, a matrix of n x n needs to be probed, where each bait is also a prey.

Protein-protein interaction networks

- Pros of Y2H:
  - Scalable



- Cons of Y2H:
  - High false positive and negative rate (as high as 50%)
  - Thus, our computational methods must be robust to noise in the data
  - Why so much noise?

  Because Y2H investigates interactions between:
  - over expressed
  - artificial, fusion proteins
  - in the yeast
  - in the yeast's *nucleus*

  Each of these steps is noisy.

  E.g.: proteins need to be in their native environment, not in nucleus

  Thus, PPIs between membrane proteins are underrepresented.