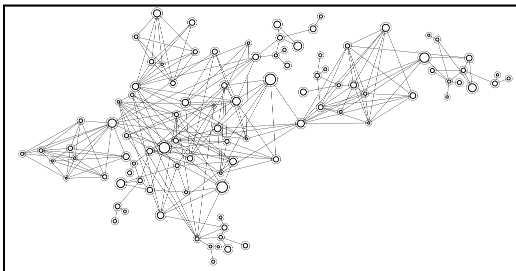
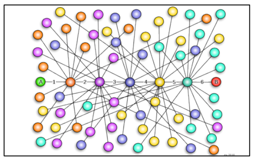


Network science in biology

measuring, visualizing and modelling real world complex networks

Petra Vertes

Quiz (1)



1. **Milgram's experiment only looked at getting letters from Nebraska to Boston. If he had kept the target in Boston but looked at starting nodes from all over the world (including tribes in remote tropical regions) do you think he would have found:**

a) A longer average path length?
b) A shorter average path length?

2. **If he had chosen the target node to be a very well-connected hub, would he have found:**

a) A longer average path length?
b) A shorter average path length?

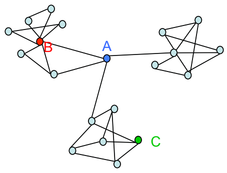
Quiz (2)

1. **Which node has higher degree, A or B?**
   a) node A has higher degree
   b) node B has higher degree

2. **Which node has higher betweenness centrality, A or B?**
   a) node A has higher betweenness centrality
   b) node B has higher betweenness centrality

3. **What is the (minimum) path-length between node A and C**
   a) $L_{A,C}=1$
   b) $L_{A,C}=2$
   c) $L_{A,C}=3$

4. **Do you think nodes A and C are in the same module?**
   a) Yes
   b) No



Superfamilies

Alon (2004) showed that the frequency signatures of network motifs classify networks into *superfamilies*.

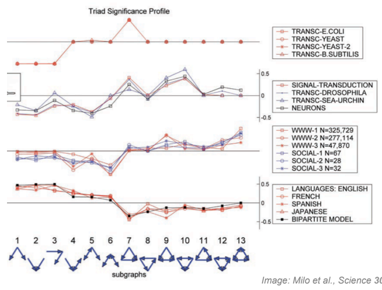
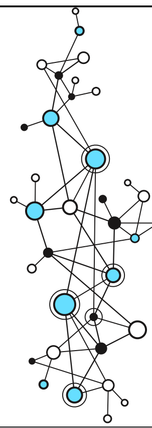


Image: Milo et al., Science 303, 1538 (2004)



Overview of topics

1. What is a network? – examples from social and biological sciences.
2. Constructing and representing complex networks.
3. Topological properties of networks – how to measure them and why they matter?
4. Network analysis in biological sciences – six examples
5. Generative modelling of networks – why and how?
6. Getting hold of data and code – tools and resources for network analysis

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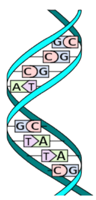
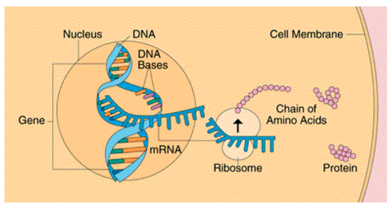
Reminder: from gene to protein





gene ⟶ protein

Where do amino acids come from?

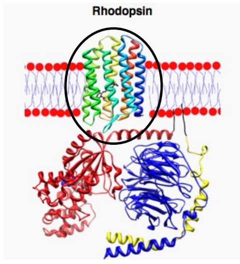
Non-essential amino acids are amino acids that your body can create out of other chemicals found in your body. Essential amino acids cannot be created, and therefore the only way to get them is through food.

- **Non-essential**
- Alanine (synthesized from pyruvic acid)
- Arginine (synthesized from glutamic acid)
- Asparagine (synthesized from aspartic acid)
- Aspartic Acid (synthesized from oxaloacetic acid)
- Cysteine
- Glutamic Acid (synthesized from oxoglutaric acid)
- Glutamine (synthesized from glutamic acid)
- Glycine (synthesized from serine and threonine)
- Proline (synthesized from glutamic acid)
- Serine (synthesized from glucose)
- Tryosine (synthesized from phenylalanine)

Essential
- Histidine
- Isoleucine
- Leucine
- Lysine
- Methionine
- Phenylalanine
- Threonine
- Tryptophan
- Valine

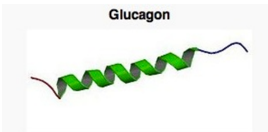
Examples of Proteins (1)

Rhodopsin, also known as visual purple, is a biological pigment in photoreceptor cells of the retina that is responsible for the first events in the perception of light.



Examples of Proteins (2)

Glucagon is a hormone, produced by the pancreas, that raises the concentration of glucose in the bloodstream. Its effect is opposite that of insulin, which lowers the glucose concentration.



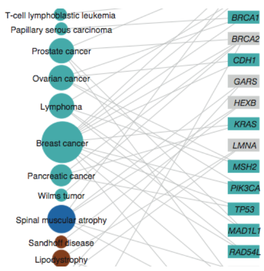
4.

Networks in Biology

(Cell biology 101)
1. Protein-protein interaction networks
2. Epistasis interaction networks
3. The diseasome
4. Drug target networks
5. Coexpression networks
6. Brain networks

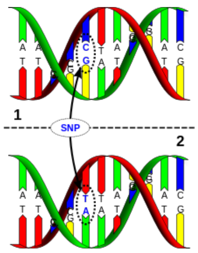
The diseasome

The bipartite network of *diseases* and *disease-related genes* is also known as the *diseasome*.



Goh et al. PNAS 104, 8685 (2007).

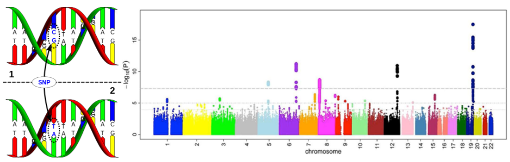
Single Nucleotide Polymorphisms (SNPs)



- A SNP is a DNA sequence variation occurring commonly within a population.
- These genetic variations underlie differences in our susceptibility to disease.
- For example, a SNP in the APOE gene is associated with a higher risk for Alzheimer disease.

Genome-wide association studies - GWAS

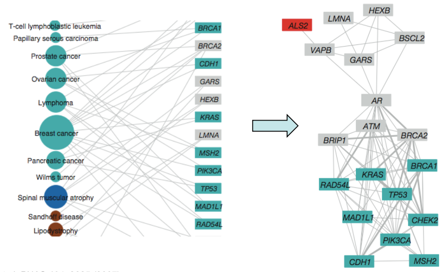
A genome-wide association study (GWAS) is an examination of many common genetic variants in different individuals to see if any variant is associated with a trait. GWAS typically focus on associations between single-nucleotide polymorphisms (SNPs) and traits like major diseases.



An illustration of a Manhattan plot depicting several strongly associated risk loci. Each dot represents a SNP, with the X-axis showing genomic location and Y-axis showing association level. In this example the peaks indicates genetic variants that are more often found in individuals with constrictions in small blood vessels.

Disease Gene Network

The *projection* of the diseasome onto disease genes, creates a *Disease Gene Network* (DGN).



Goh et al. PNAS **104**, 8685 (2007).

Disease Gene Network & Protein-protein Interaction Network

Gene A — Gene B

Changes in both genes are risk factors for the same disease

Protein A — Protein B

The two proteins interact with each other physically in the cell

Gene A — Gene B

Protein A Protein B

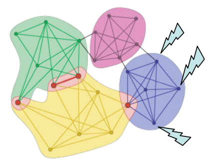
Gene A Gene B

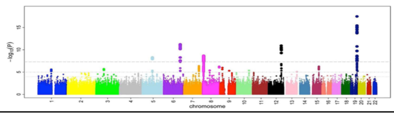
Protein A — Protein B

Network-based prediction of disease genes (network medicine)

Mapping the disease genes onto the protein interaction network can help identify related proteins/genes that might also be implicated in the same disease but which GWAS failed to pick up.

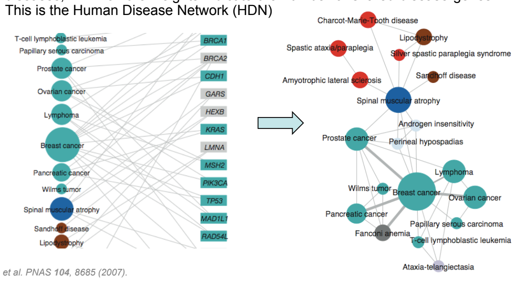
The problem of multiple comparison sets very stringent statistical thresholds on GWAS, meaning many real associations may be missed.





Human Disease Network

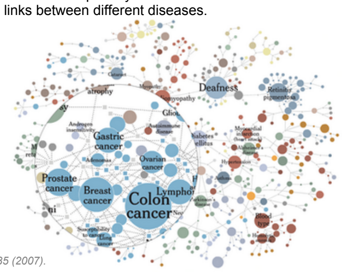
Similarly, projecting the diseasome onto diseases yields a weighted network of diseases, in which the weights indicate the number of shared disease genes. This is the Human Disease Network (HDN)



Goh et al. PNAS **104**, 8685 (2007).

Human Disease Network

The Human Disease Network forms a giant component with 516 out of 1284 disorders. It has eight times as many connections between disorders of the same class than we would expect by chance. Some of these connections may reveal unknown links between different diseases.



Goh et al. PNAS **104**, 8685 (2007).

4.

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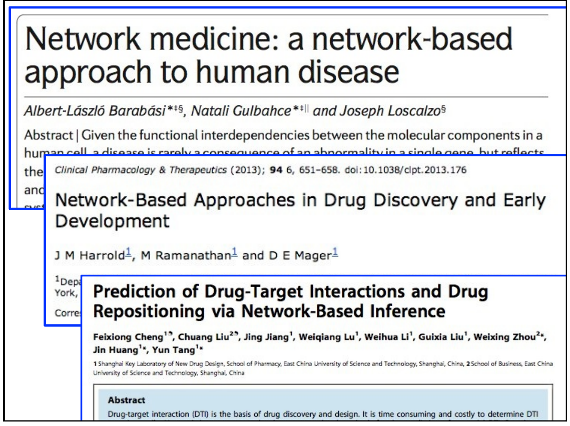
6. Brain networks

Drug-target networks

Yildirim et al (2007) Nature



Network medicine: a network-based approach to human disease

*Albert-László Barabási**‡§*, Natali Gulbahce**‡‖ *and Joseph Loscalzo*§

Abstract | Given the functional interdependencies between the molecular components in a

Clinical Pharmacology & Therapeutics (2013); **94** 6, 651–658. doi:10.1038/clpt.2013.176

Network-Based Approaches in Drug Discovery and Early Development

J M Harrold[1], M Ramanathan[1] and D E Mager[1]

Prediction of Drug-Target Interactions and Drug Repositioning via Network-Based Inference

Feixiong Cheng[1], Chuang Liu[2], Jing Jiang[1], Weiqiang Lu[1], Weihua Li[1], Guixia Liu[1], Weixing Zhou[2]*, Jin Huang[1]*, Yun Tang[1]*

1 Shanghai Key Laboratory of New Drug Design, School of Pharmacy, East China University of Science and Technology, Shanghai, China, 2 School of Business, East China University of Science and Technology, Shanghai, China

Abstract

Drug-target interaction (DTI) is the basis of drug discovery and design. It is time consuming and costly to determine DTI

4.

Networks in Biology

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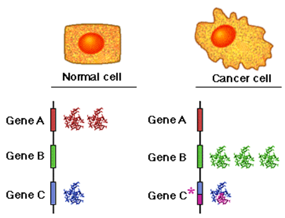
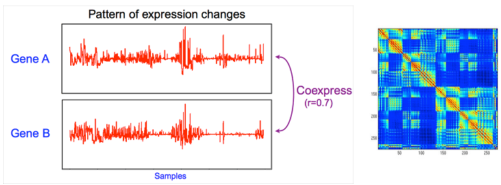
Differential Gene Expression



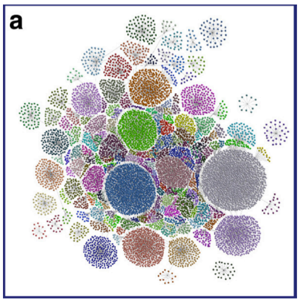
Obtain long list of differentially expressed genes – no context

Coexpression

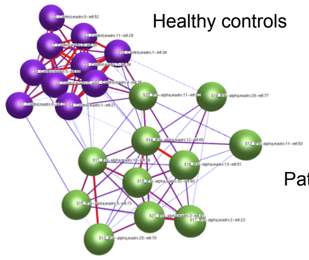


Different samples may be different subjects, different cell types, same cell at different times, etc.

Coexpression (gene) networks



Coexpression (sample) networks



Note: There is great interest in finding sub-groups of patients that may need different treatment

4.

Networks in Biology

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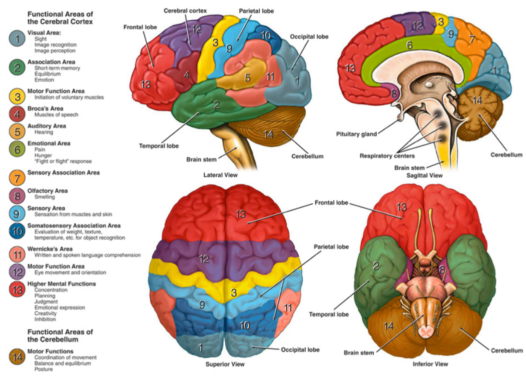
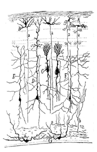
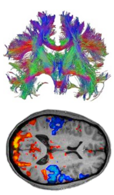
Anatomy and Functional Areas of the Brain



The brain as a network



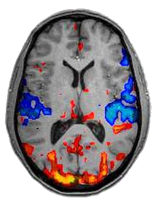
Networks of neurons



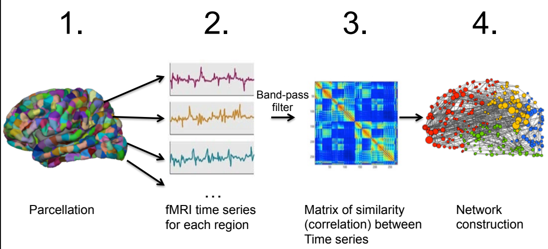
Large-scale anatomical and functional connectivity of brain regions

Functional Magnetic Resonance Imaging (fMRI)

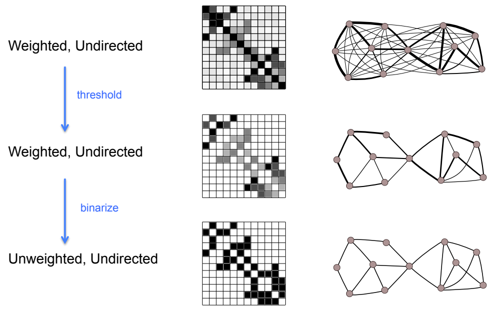
Functional magnetic resonance imaging (fMRI), provides a 3D snapshot of brain activity every one or two seconds by measuring blood flow in the brain. The spatial resolution is limited to voxels of a few cubic millimeters.



Constructing fMRI Brain Networks



Thresholding and Binarizing



Goals of brain network analysis

1. Describe healthy brain networks
2. Linking structure and function
3. Help describe & understand disease
4. Help measure the effect of drugs

Goals of brain network analysis

Optimistic progress bar

1. Describe healthy brain networks
2. Linking structure and function
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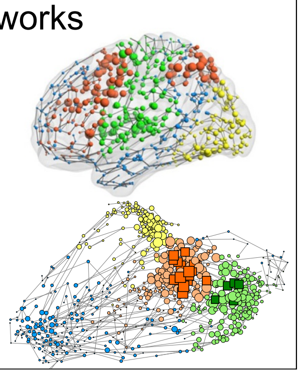
Quiz (3)

Do you think healthy brain functional networks are:

1. More or less clustered and a random network?
2. More or less modular than a random network?
3. Small-world?
4. Scale-free (or similar)?

Describing healthy brain networks

1. Small-world
2. Hubs
3. Modules
4. Core-periphery
5. Economy of wiring



Bullmore & Sporns (2009) *Nat Rev Neurosci*
Van den Heuvel et al (2012) *PNAS*

Goals of brain network analysis

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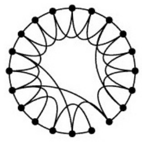
Optimistic progress bar

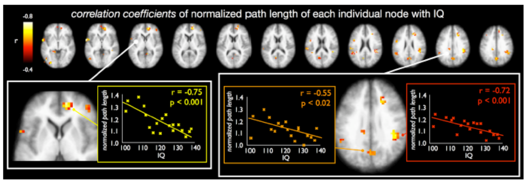
A brain is an expensive machine

- Human brain is about 2% of body mass but consumes about 20% of the body's energy budget
- Many aspects of brain anatomy nearly minimize wiring or connection cost



Expensive, long-range connections may be "worth it"

Greater efficiency (or shorter path length) of human brain networks is correlated with higher IQ:



Van den Heuvel et al (2009) *J Neurosci*
Li et al (2009) *PLoS Comp Biol*

Goals of brain network analysis

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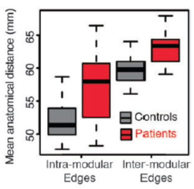
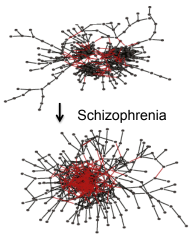
Optimistic progress bar

Schizophrenia: more long distance connections, less modularity

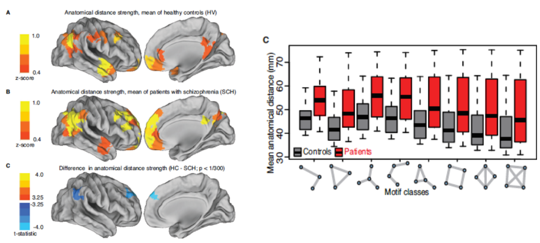




Alexander-Bloch et al (2012) *Cereb Cortex*
Alexander-Bloch et al (2012) *NeuroImage*

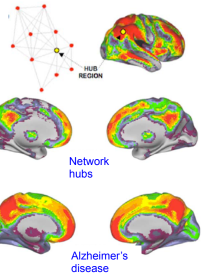
Intra-modular edges
Inter-modular edges

Zooming-in on topological differences in schizophrenia



Alexander-Bloch et al (2011) *Cereb Cortex*

The role of network hubs in Alzheimer's Disease



Buckner et al (2009) *Journal of Neuroscience*

Goals of brain network analysis

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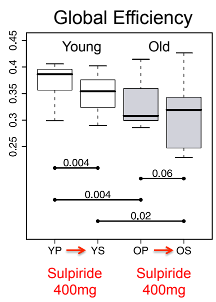
4. Help measure the effect of drugs

Optimistic progress bar

The effect of Sulpiride on healthy volunteers

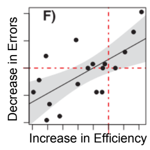
Sulpiride significantly reduces the Global Efficiency of healthy brain networks, counteracting the subtle randomization seen in schizophrenia



Achard & Bullmore (2007) *PLoS Comp Bio*

Effect of Nicotine on networks and behaviour

- Improves reaction times
- Reduces errors in error-prone subjects
- Decreases Clustering
- Increases Efficiency



Giessing et al (2012) *J Neurosci*

Goals of brain network analysis

Optimistic progress bars

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Challenges for fMRI/DTI network analysis

1. Methodological issues:
   - Acquisition: DTI distance effect, motion, …
   - Preprocessing
   - Measures of association: spurious correlations (silencing?)
2. Sensitivity of network measures:
   - Group differences for less severe diseases
   - Diagnosis of individuals
3. Specificity of network measures:
   - Increased E: with high IQ, with Nicotine, in schizophrenia…
   - Decreased E: with age, in Alzheimer's disease, with Sulpiride…

Brain network analysis and modelling