Biological networks
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University of Zurich[UZH]

Session 1 (45 min): Examples of biological networks

Session 2 (45 min): Properties of networks

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Session 1

Examples of biological networks

What is a network?

Two or more components that can “interact” with each other

Biological networks

Networks that apply to biological systems:

1) DNA
2) Protein
3) Cell
4) Organisms
5) …..

DNA and Proteins

DNA

Myoglobin
(PDB=3RGK)

Chemical structures (networks)

Chemical vs. Biological views

Chemical structures

Contact map (Biological)

Protein-protein interaction network

Example:
Pol II complex
(PDB=1Y1W)

Protein-protein interaction network

Compare the interaction networks of two proteins in human:

- Myoglobin (Mb)
- DNA-directed RNA polymerase II (RPB1)

Why do we have different tissues and cell types if we have only one DNA molecule?

Gene regulatory networks
(DNA-protein interaction networks)

(GRN)

A set of molecular **regulators** that interact with each other to govern the **gene expression** levels of mRNA and proteins >> the **function** of the **cell**.

Responses to stress often involve co-expression of many genes. How do cells achieve this coordinated response?

Gene co-expression network

(GCN)

A gene co-expression network can be built by finding pairs of genes which show a similar expression pattern across samples.

Gene co-expression network

RNA-seq
or
Microarray
experiments

	S_1	S_2	S_3
G_1	43.26	40.89	5.05
G_2	166.6	41.87	136.65
G_3	12.53	39.55	42.09
G_4	28.77	191.92	236.56
G_5	114.7	79.7	99.76
G_6	119.1	80.57	114.59
G_7	118.9	156.69	186.95
G_8	3.76	2.48	136.78
G_9	32.73	11.99	118.8
G_{10}	17.46	56.11	21.41

Gene expression values

$\xrightarrow{|r(G_i,G_j)|}$

Pearson correlation

	G_1	G_2	G_3	G_4	G_5	G_6	G_7	G_8	G_9	G_{10}
G_1	1.00	0.23	0.61	0.71	0.03	0.35	**0.86**	**1.00**	**0.97**	0.37
G_2	0.23	1.00	0.63	0.52	**0.98**	**0.99**	0.29	0.30	0.46	**0.99**
G_3	0.61	0.63	1.00	**0.99**	0.77	0.53	**0.93**	0.56	0.41	0.51
G_4	0.71	0.52	**0.99**	1.00	0.69	0.41	**0.97**	0.66	0.52	0.40
G_5	0.03	**0.98**	0.77	0.69	1.00	**0.95**	0.48	0.09	0.27	**0.94**
G_6	0.35	**0.99**	0.53	0.41	**0.95**	1.00	0.17	0.41	0.57	**1.00**
G_7	0.86	0.29	**0.93**	**0.97**	0.48	0.17	1.00	**0.83**	0.72	0.16
G_8	**1.00**	0.30	0.56	0.66	0.09	0.41	0.83	1.00	**0.98**	0.42
G_9	**0.97**	0.46	0.41	0.52	0.27	0.57	0.72	**0.98**	1.00	0.58
G_{10}	0.37	**0.99**	0.51	0.40	**0.94**	**1.00**	0.16	0.42	0.58	1.00

Similarity (Co-expression) score

$\longleftarrow$

	G_1	G_2	G_3	G_4	G_5	G_6	G_7	G_8	G_9	G_{10}
G_1	0	0	0	0	0	0	1	1	1	0
G_2	0	0	0	0	1	1	0	0	0	1
G_3	0	0	0	1	0	0	1	0	0	0
G_4	0	0	1	0	0	0	1	0	0	0
G_5	0	1	0	0	0	1	0	0	0	1
G_6	0	1	0	0	1	0	0	0	0	1
G_7	1	0	1	1	0	0	0	1	0	0
G_8	1	0	0	0	0	0	1	0	1	0
G_9	1	0	0	0	0	0	0	1	0	0
G_{10}	0	1	0	0	1	1	0	0	0	0

Network adjacency matrix

$\xleftarrow{|r(G_i,G_j)|>=0.8}$

Significance threshold

Metabolic networks

A metabolic network is a set of chemical reactions that produces

energy
(for maintenance of cell functions and for biosyntheses)

molecular building blocks for biosyntheses

These reactions are catalyzed by enzymes that are encoded by genes.

In free-living heterotrophic organisms, several hundred such enzymatic reactions are necessary to fulfill these functions.

Metabolic networks

Metabolic networks

Find the folate biosynthetic pathway in Human and *E.coli*

Database 2: KEGG

Folate pathway

Arrows are reactions

Enzymes

Nodes are metabolites

Folate pathway in E.coli and Human

E.coli

Human

Biological and other complex networks may have similar structures

Metabolic map

New York subway map

(Obviously!) cells should communicate.
How do they achieve this?

Signaling networks

*Scientific reports*8.1 (2018): 1-11.

reactome

About Content Docs Tools Community Download

Find Reactions, Proteins and Pathways

e.g. O95631, NTN1, signaling by EGFR, glucose Go!

Pathway Browser

Visualize and interact with Reactome biological pathways

Analysis Tools

Merges pathway identifier mapping, over-representation, and expression analysis

ReactomeFIViz

Designed to find pathways and network patterns related to cancer and other types of diseases

Documentation

Information to browse the database and use its principal tools for data analysis

Database 3: RACTOME

Any higher-level network to talk about?

Food web

Yellow node: top species or primary predators.

Orange nodes: represent intermediate species

Red nodes: basal species, such as plants.

Session 2

Properties of networks

Graphs

A graph G=(V,E) comprises
a set V of nodes (vertices)
a set E of edges

$$V = \{V_1, \ldots, V_n\}$$
$$E = \{(V_i, V_j), \ldots, (V_k, V_l)\}$$

Protein interaction networks are <u>undirected</u> graphs
(Individual node pairs in *E* are unordered.)

Graphs

A <u>path</u> is a sequence of alternating nodes and edges in which no node is visited more than once

A <u>geodesic</u> is the shortest path between two nodes.

Graphs can be represented by matrices

Adjacency matrix $A=(a_{ij})$

$a_{ij}=1$ $(V_i, V_j) \in E$

$a_{ij}=0$ otherwise

$$A = \begin{pmatrix} 0 & 1 & 0 & 0 & 0 & 1 & 1 \\ 1 & 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 & 1 & 1 & 0 \\ 0 & 0 & 1 & 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 1 & 0 & 1 & 0 \\ 1 & 1 & 1 & 0 & 1 & 0 & 1 \\ 1 & 0 & 0 & 0 & 0 & 1 & 0 \end{pmatrix}$$

Class activity:

Determine the degree distribution of your network of friends (n=5)

plot(sample_k_regular(10, 2))

plot(sample_k_regular(10, 3))

plot(sample_k_regular(10, 4))

Degree distribution can help us determine the type of networks

Fig. 6 Shape and degree distribution of random, small-world, and scale-free model with respect to a biological network. Models were calculated by ELIXIR web tool [131]

EURASIP Journal on Bioinformatics and Systems Biology 2017.1 (2017): 1-16.

Class activity:

How do you build a random graph?

The random graph

Erdős–Rényi model

$$P(k) = \binom{n-1}{k} p^k (1-p)^{n-1-k}$$

$$P(k) = e^{-(np)} \frac{(np)^k}{k!}$$

plot(sample_gnp(30, 0.01))

plot(sample_gnp(30, 0.1))

plot(sample_gnp(30, 0.5))

The random graph

*n.p=100*0.1=100*

Degree distribution of graphs

The degree (connectivity) k_i of a node V_i is the number of edges incident with the node (e.g., k_1=3, k_6=5).

$$k_i = \sum_j a_{ij}$$

Graphs can be characterized according to their degree distribution P(k), the fraction of nodes having degree k.

Connectivity can affect the evolution of proteins!

Highly connected proteins tolerate fewer amino acid substitutions in their evolution

Hahn et al. Journal of Molecular Evolution 2004

Are biological networks random?

Biological network are non-random

Transcriptional regulatory network

Genetic interaction network

Metabolic networks have a broad-tailed degree distribution

Substrate network of E. coli

Wagner and Fell, Proc. Roy. Soc. London B 2001

The random graph vs. scale-free graph

Linear-linear scale

The random graph vs. scale-free graph

Log-log scale

What is so special about scale-free networks?

Nearest-neighbor degree of nodes

Average nearest neighbor degree of a node

$k_1=3$

$k_2=5$

$k_3=5$

$k_4=2$

$k_{nn,1}=(1/3)(5+5+2)=4$

$$k_{nn,i} = \frac{1}{k_i} \sum_{\text{j, nearest neighbors of i}} k_j$$

Assortative vs. Disassortative networks

Average nearest neighbor degree of all nodes with degree *k*

$$k_{nn,i} = \frac{1}{k_i} \sum_{\text{j, nearest neighbors of i}} k_j$$

N_k ...number of nodes with degree k

$$k_{nn}(k) = \frac{1}{N_k} \left(\sum_{\text{nodes with degree } k} k_{nn,k} \right)$$

A graph is <u>assortative</u> if $k_{nn}(k)$ increases with k

nodes connect to nodes of similar connectivity

A graph is <u>disassortive</u> if $k_{nn}(k)$ decreases with k

Assortative vs. Disassortative networks

Class activity:

With only three choices, how would you i) <u>preserve</u> and ii) <u>decrease</u> the <u>disassortative</u> nature of the graph.

Protein interaction networks are disassortative

Few interactions between hubs

Many interactions between hubs and neighbors with low degree

Plot of $P_{nn}(k)$ against k for the yeast protein interaction network (triangles) and the transcriptional regulation network (squares)

Maslov and Sneppen, Science 2002

Measures of graph compactness: path length and diameter

Matrix of shortest paths D=(d_{ij})

$$D = \begin{pmatrix} 0 & 1 & 2 & 3 & 2 & 1 & 1 \\ 1 & 0 & 2 & 3 & 2 & 1 & 2 \\ 2 & 2 & 0 & 1 & 1 & 1 & 2 \\ 3 & 3 & 1 & 0 & 1 & 2 & 3 \\ 2 & 2 & 1 & 1 & 0 & 1 & 2 \\ 1 & 1 & 1 & 2 & 1 & 0 & 1 \\ 1 & 2 & 2 & 3 & 2 & 1 & 0 \end{pmatrix}$$

Connected graph: $d_{ij} < \infty$ for all i,j

Betweenness centrality

Measure of centrality in a graph based on shortest path

- σ_{uw} — # of shortest path between nodes *u* and *w*
- $\sigma_{uw}(v)$ — # of shortest path between nodes *u* and *w* that involve *v*

$\sigma_{AB} = 1$

$\sigma_{AB}(C) = 0$

Betweenness centrality

$$= \frac{\sigma_{uw}(v)}{\sigma_{uw}}$$

Betweenness centrality

Related to the class on 09.11.2021:

Note related to the class on 09.11.2021: This is the **number of shortest paths** and not **the number of edged** between the two nodes

$$\sigma_{AB} = 1$$
$$\sigma_{AB}(C) = 0$$

Betweenness centrality

	σ_{uw}	$\sigma_{uw}(v)$	$\sigma_{uw}(v)/\sigma_{uw}$
(A,B)	1	0	0
(A,D)	1	1	1
(A,E)	1	1	1
(A,F)	1	1	1
(B,D)	1	1	1
(B,E)	1	1	1
(B,F)	1	1	1
(D,E)	1	0	0
(D,F)	1	0	0
(E,F)	1	0	0

Sum=6

Betweenness centrality

What is the betweenness centrality of the node F ?

Bottlenecks have high betweenness centrality scores

Proteins with high betweenness scores tend to be more essential

Advanced topics: Graphs can be subdivided into “communities”

Community structure of a rat protein interaction network

Fortunato and Hric, Physics Reports 659, 1-44, 2016

Advanced topics: Graphs can be subdivided into “communities”

In a graph that can be subdivided into
communities (clusters, modules)
nodes fall into groups that
share more edges with each other than
with nodes outside the community

Fortunato and Hric, Physics Reports 659, 1-44, 2016

Advanced topics: Graphs can be subdivided into “communities”

Some require information about the total number of communities (easier), others don’t (more difficult).

Hard-clustering methods generate non-overlapping communities (easier)

Soft-clustering methods allow overlapping communities (more difficult)

Advanced topics: We can do calculations with graphs

A chemical reaction network

Metabolite concentrations m_i change according to the equations

$$\frac{dm_1}{dt} = v_s - v_1 - v_2$$
$$\frac{dm_2}{dt} = v_1 + v_3 - v_p$$
$$\frac{dm_3}{dt} = v_2 - v_3$$

$$\frac{d\vec{m}}{dt} = \mathbf{S}\vec{v}$$

$$\mathbf{S} = \begin{pmatrix} 1 & -1 & -1 & 0 & 0 \\ 0 & 1 & 0 & 1 & -1 \\ 0 & 0 & 1 & -1 & 0 \end{pmatrix}$$

Stoichiometry matrix

v_i metabolic flux through reaction i

$$\vec{v} = (v_s, v_1, v_2, v_3, v_P)^\top$$

Rows: metabolites
Columns: reactions

Advanced topics: We can do calculations with graphs

FBA assumes that metabolism is in a steady state where the concentrations of metabolites no longer change

$$\frac{d\vec{m}}{dt} = 0$$

$$\mathbf{S}\vec{v} = 0$$

The solutions of these equations are the allowable metabolic fluxes. They form the so-called <u>null space of S</u>

Advanced topics: Network medicine

Frontiers in Genetics 10 (2019): 294.

Concluding remarks

- Networks are everywhere! Biological systems also behave as interconnected networks.
- Several mathematical approaches and disciplines such as graph theory help us model networks.
- We don’t just visualize networks. We also use networks for:
  - Quantitative analyses
  - Predictions (Bayesian graph networks)
- Don’t overlook the experimental approaches to build networks!

Further reading

Complex networks in general

Newman, MEJ. The structure and function of complex networks. *SIAM Review* **45**, 167-256, 2003.

Fortunato, S., Hric, D. Community detection in networks: A user guide. *Physics Reports* **659**, 1-44. 2016.

Protein interaction networks

Xia et al. Analyzing cellular biochemistry in terms of molecular networks. *Annu. Rev. Biochem.* **73**:1051–87, 2004

Rajagopala et a., The binary protein-protein interaction landscape of *Escherichia coli. Nature Biotechnology* **32***, 285-290, 2014*

Metabolic networks

Price et al. Nature Reviews Microbiology **2**, 886-897, 2004

Exam questions

5 questions

Multiple choices

- 2 quantitative questions
  - Random graphs
  - Degree distribution
  - Betweenness centrality
- 3 descriptive questions
  - Databases
  - Types of graphs
  - Different biological networks

Related to the class on 09.11.2021:
A good tutorial on the calculation of betweenness centrality:
https://www.youtube.com/watch?v=3X29Lfm6p2s