

Introduction to Graph Theory

Proteomes Interactomes and Biological Networks

Emidio Capriotti

<http://biofold.org/>



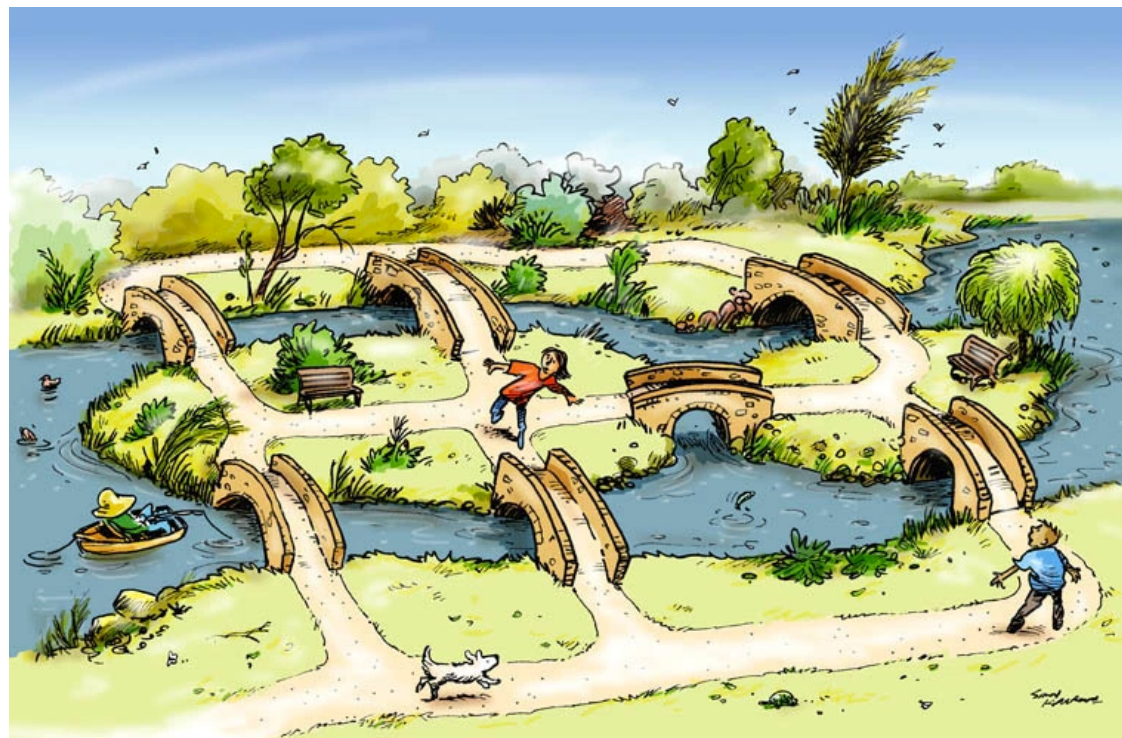
**Biomolecules
Folding and
Disease**

Department of Pharmacy and
Biotechnology (FaBiT)
University of Bologna



Historical Perspective

With the **Seven Bridges of Königsberg** problem, Euler in 1737 laid the foundations of the graph theory.

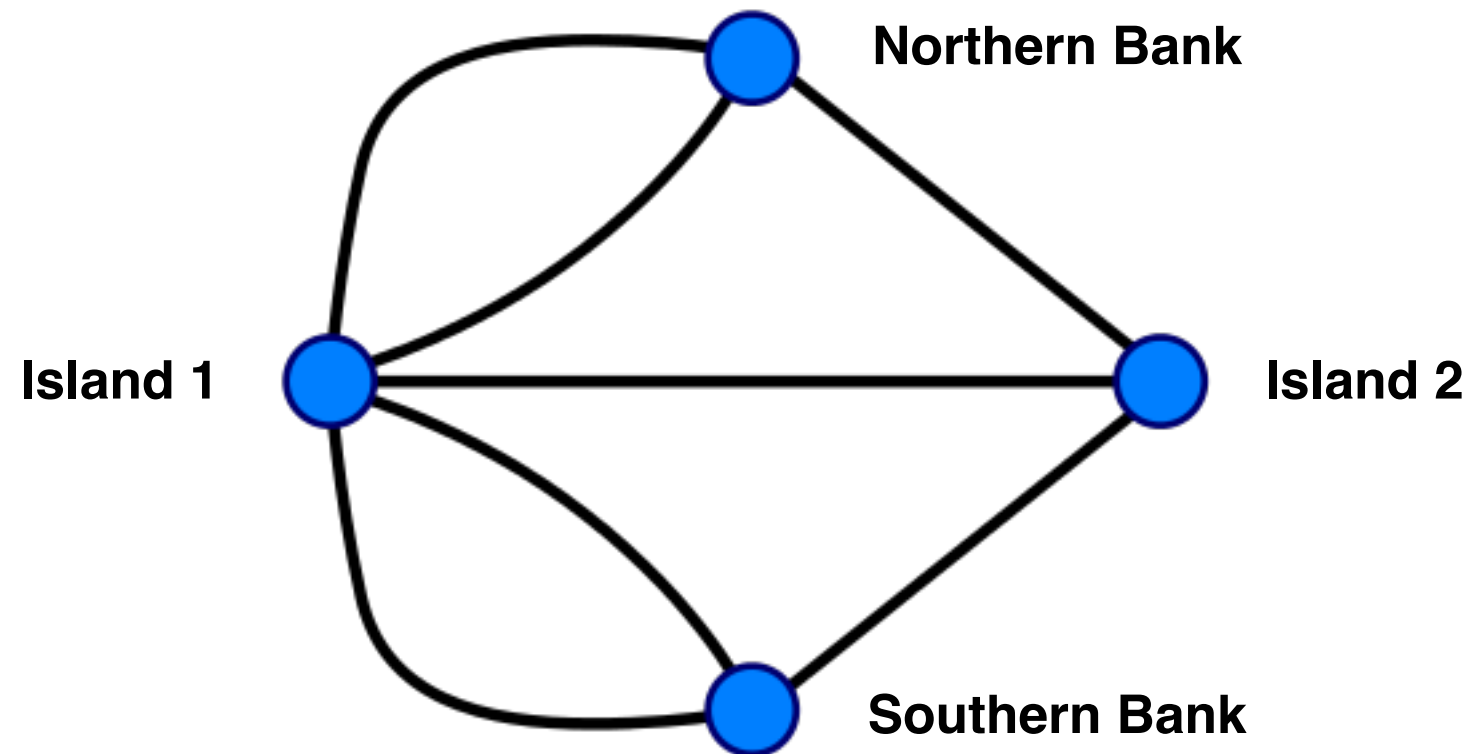


Simon Kneebone – simonkneebone.com

- Find path (Eulerian Path) that **traverses all the Pregel's bridges**.
- Find walk (Eulerian Circuit) that **traverses all the Pregel's bridges** and has **the same starting and ending point**.

Solution

Describe the problem as a graph where the **nodes represent the 4 locations** and the **edges correspond to the bridges**



Eulerian path exists only if **zero or 2 nodes** are connected by an **odd number of bridges**.

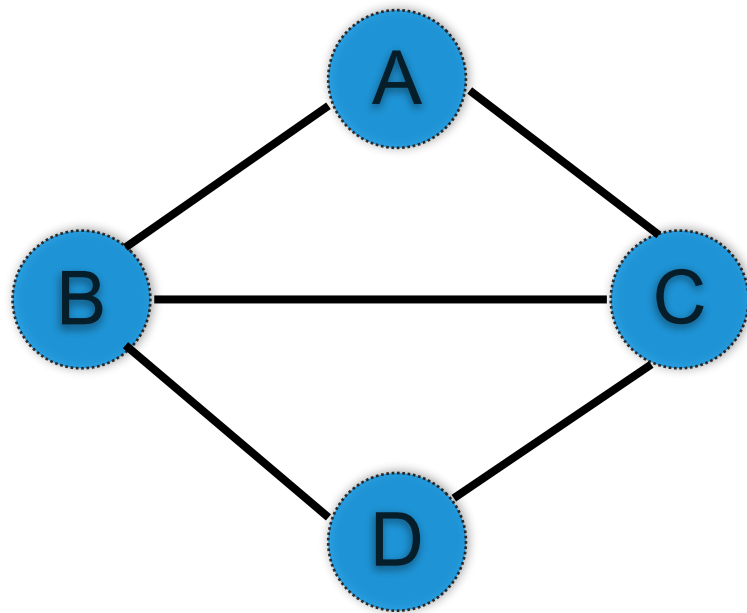
Eulerian circuit exists only if **zero nodes** are connected by an **odd number of bridges**.

Graph Definition

A graph is a pair $G=(V,E)$ consisting of two sets:

- V is a set of elements called **Nodes or Vertices**.
- E is a set of pairs (v_i, v_j) where $v_i \in V$ and $v_j \in V$.

The pairs E are links between two nodes and are called **Edges**

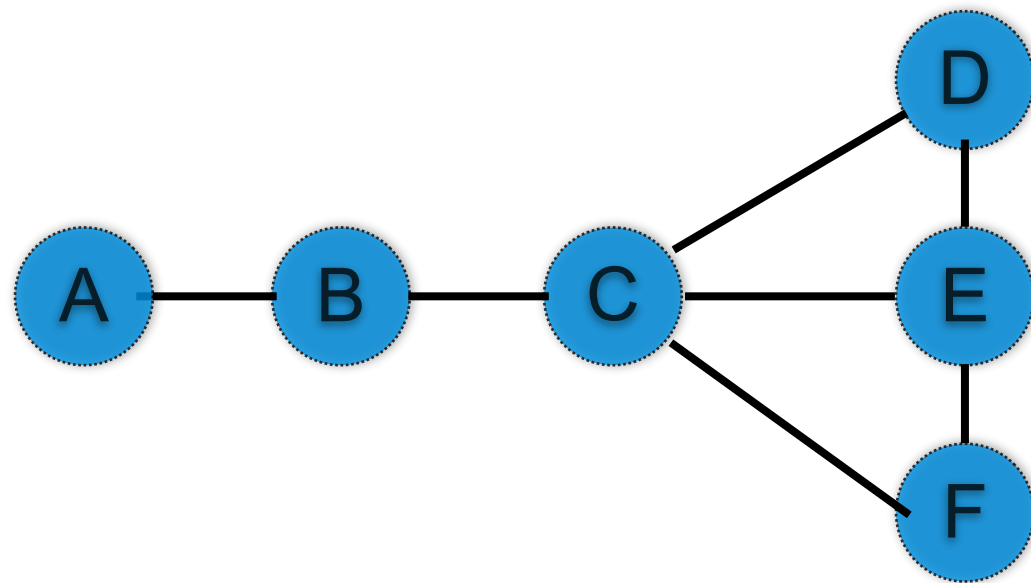


$$V = \{A; B; C; D\}$$

$$E = \{(A,B); (A,C); (B,C); (B,D); (C,D)\}$$

Undirected Graph

Undirected graph is a network where the relationship between nodes are symmetric.

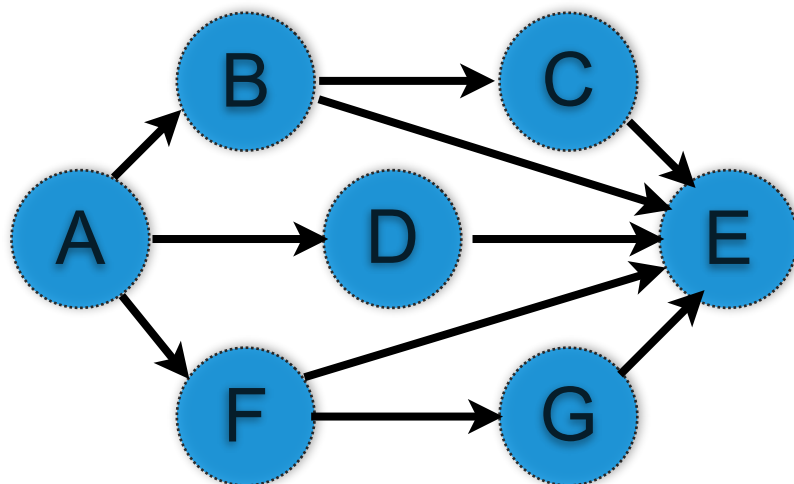
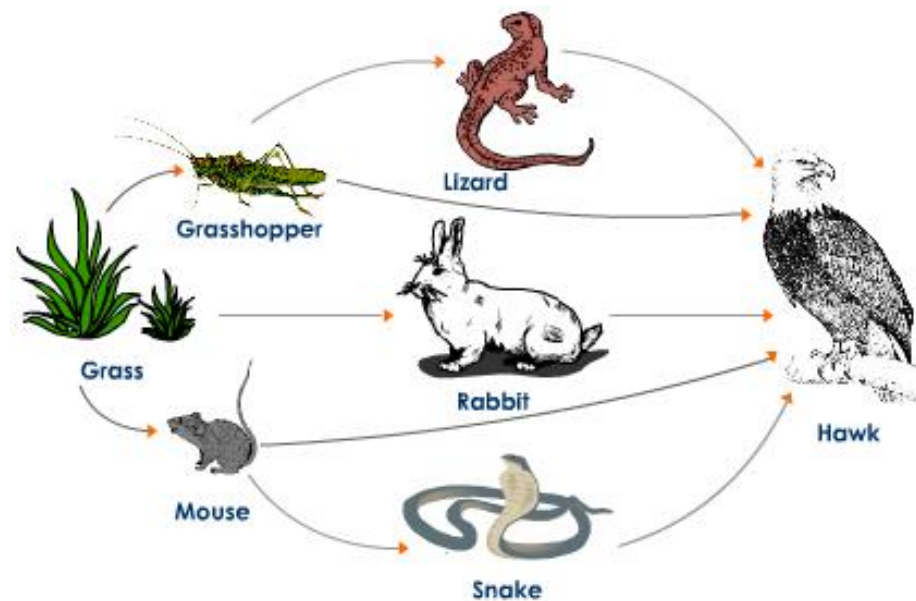


$V = \{\text{Group of People}\}$

$E = \{\text{Pairs of Friends}\}$

Directed Graph

Directed graph is a network where the relationship between nodes are asymmetric. In this case the edges are directed lines.

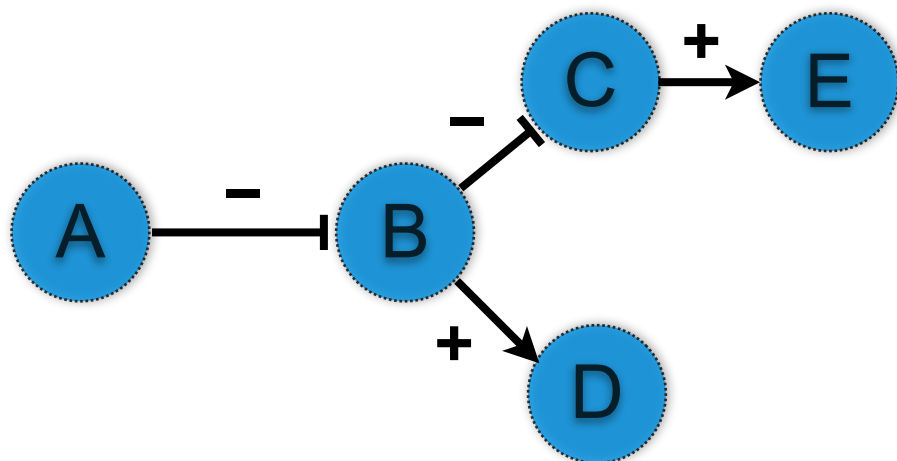
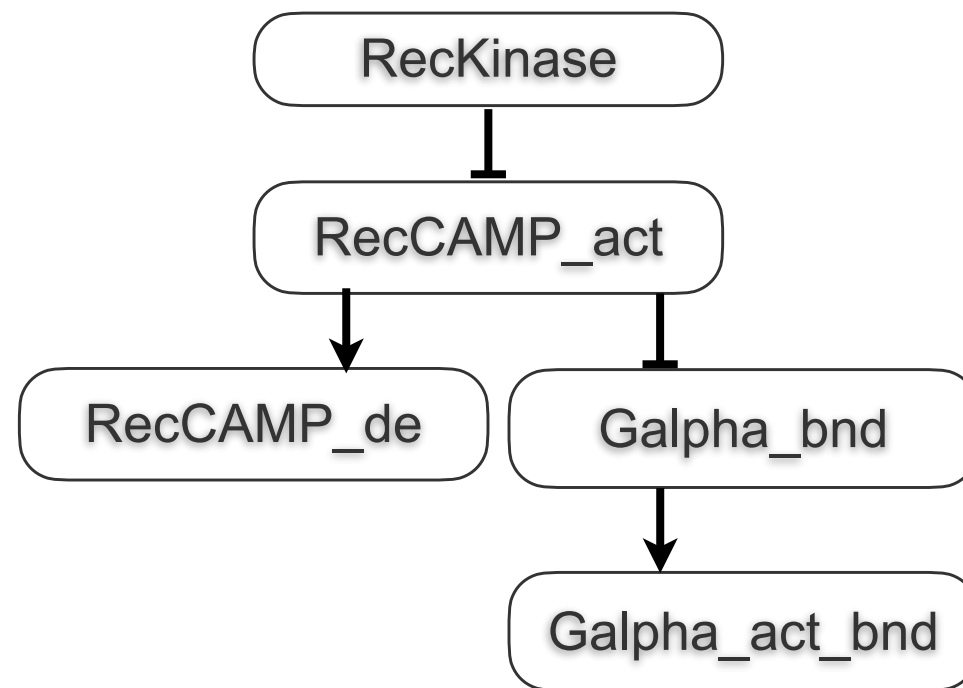


$V = \{\text{Group of Animals}\}$

$E = \{\text{Prey/Predator Relationships}\}$

Signed Directed Graph

Signed Directed graph is a network where the relationship between nodes are asymmetric and have positive or negative associated signs



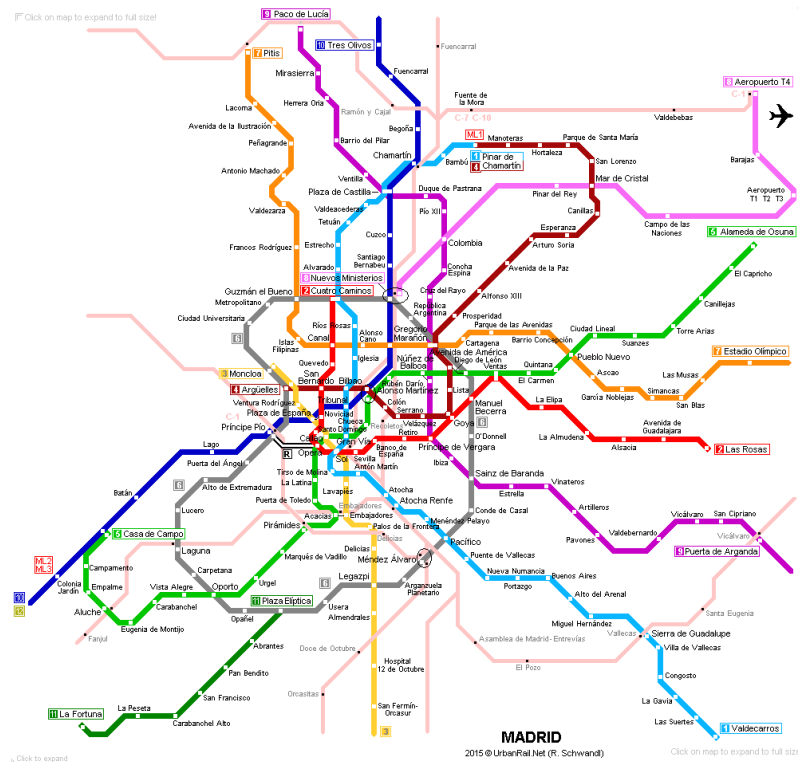
$V = \{\text{Group of Genes}\}$

$E = \{\text{Activation/Inhibition Relationships}\}$

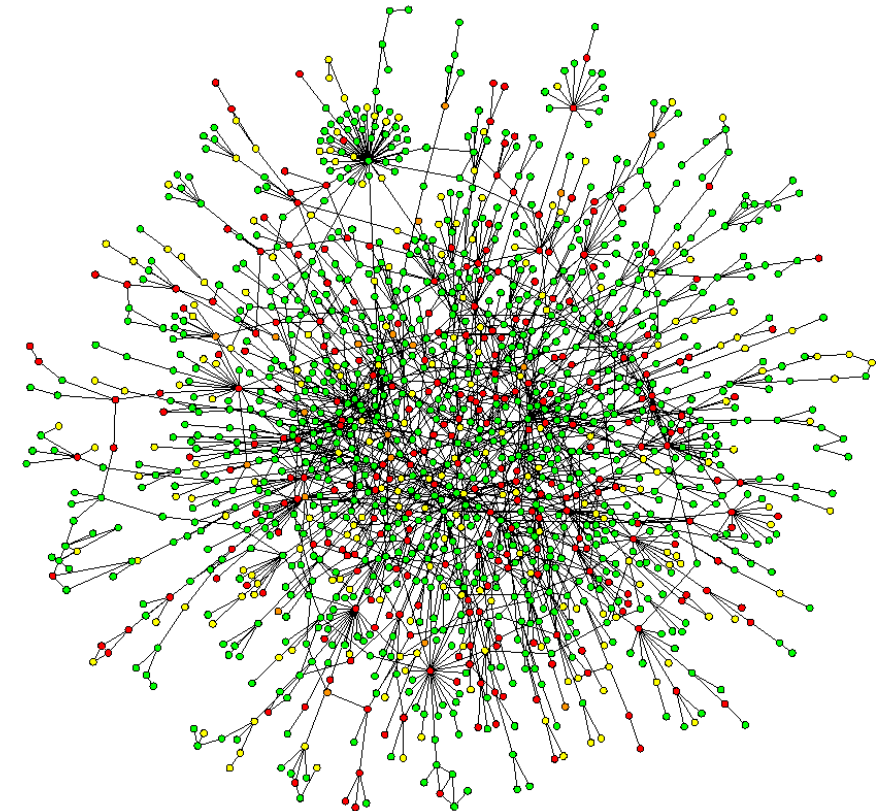
Graph and Networks

Graphs can be used to represent any observed network.

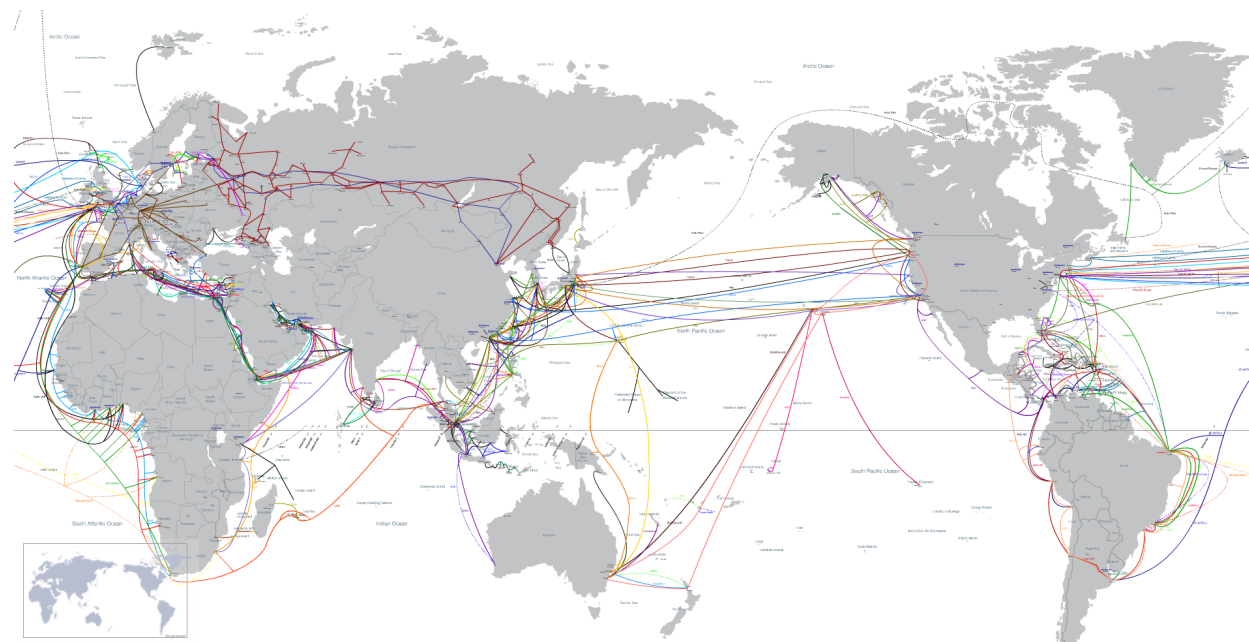
Networks in nature tend to be highly complex



Internet connections



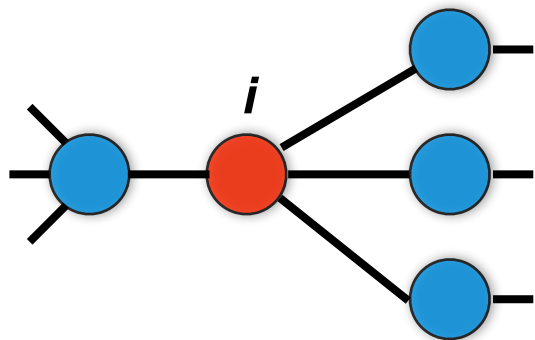
Madrid Metro



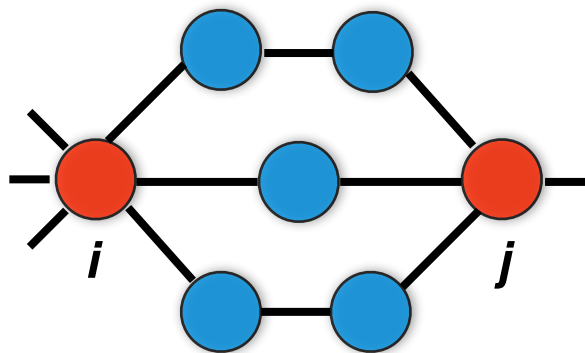
Yeast interactome

Network properties (I)

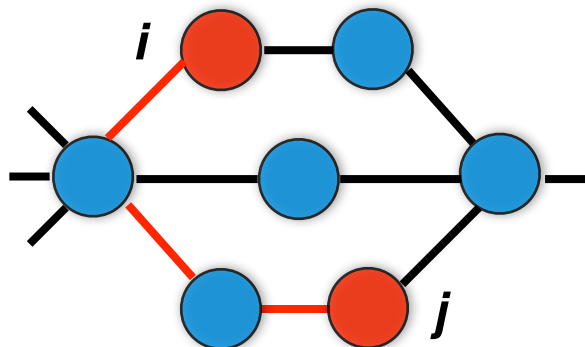
The **topology** of the network **defines its properties**. The level of **connectivity** among the nodes **depends on the number of edges**.



Degree k_i = number of links connected to node i



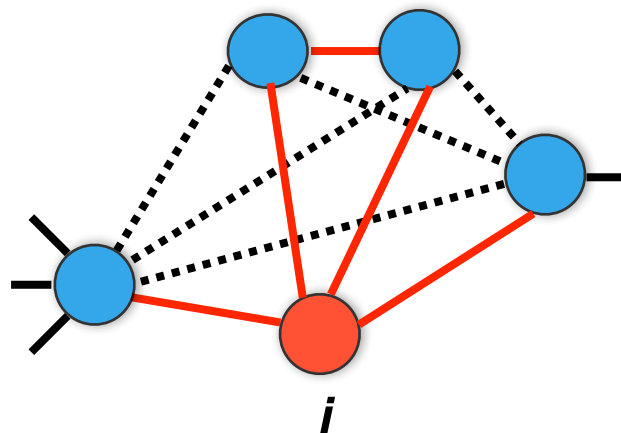
Distance d_{ij} = shortest path between nodes i and j



Diameter D = longest path between all pairs of nodes

Network properties (II)

The **topology** of the network **defines its properties**. The level of **connectivity** among the nodes **depends on the number of edges**.

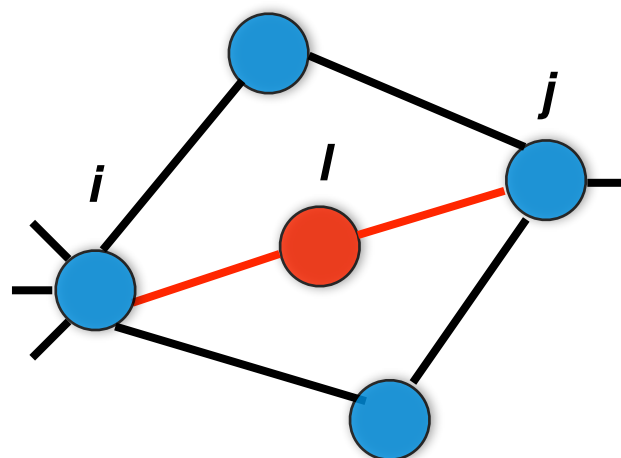


Transitivity
or
Clustering
Coefficient

$$c_i = \frac{2e_i}{k_i(k_i - 1)}$$

k_i = number of nodes connected to i

e_i = number of edges between the k_i nodes



Betweenness

$$g_l = \sum_{i \neq l \neq j} \frac{\sigma_{ij}(l)}{\sigma_{ij}}$$

σ_{in} = number of shortest path between i and j

$\sigma_{ij}(l)$ = number of shortest path passing through node l

Types of Network

The **topology** of the network depends on the **distribution of the degree** for all the nodes.

We can define three types of network:

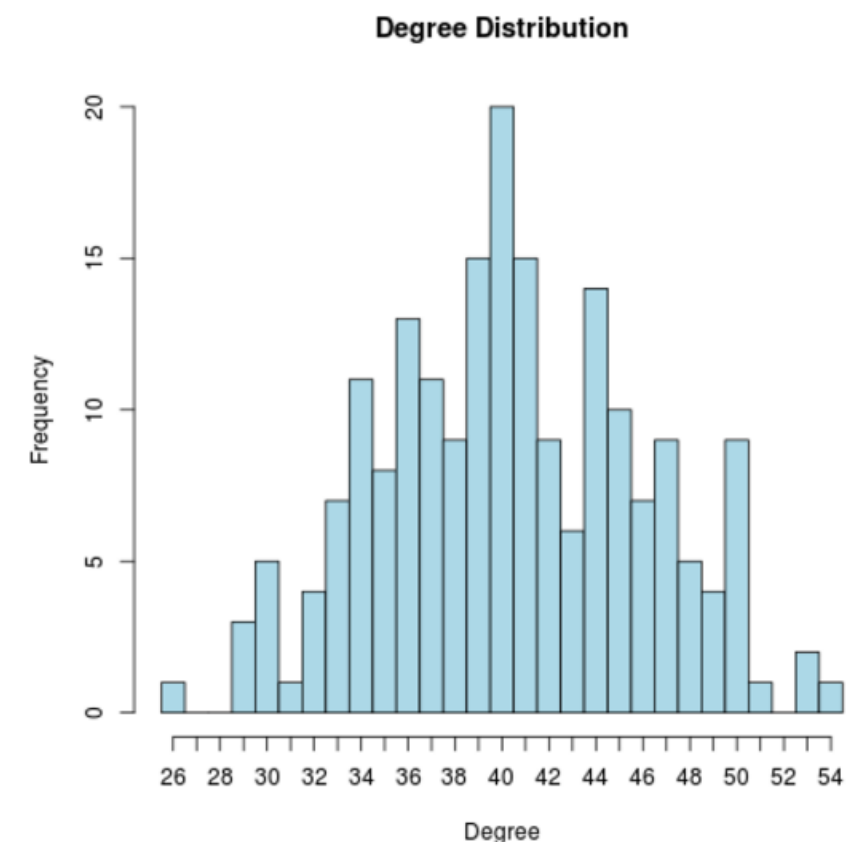
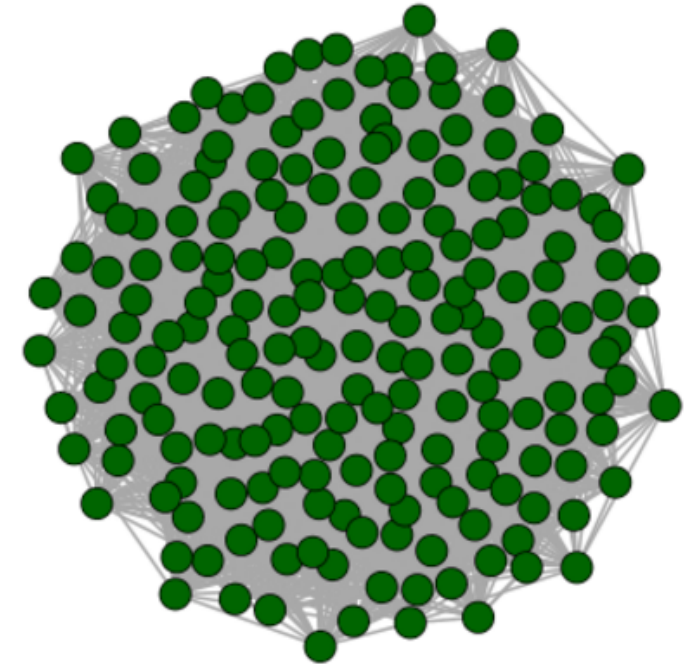
- **Random network**: generated by a constant probability of having an edge between two nodes.
- **Small-world network**: when the degrees follow a Poisson distribution
- **Scale-Free network**: the degrees follow a Power Law distribution

Random Network

Can be generated by Erdős–Rényi model which assume a **constant probability of generating edges** between nodes.

- High node degree \Rightarrow **low average path length**
- Degree **distribution tends to be a Gaussian**
- High Transitivity
- Small Betweenness

Degree = 40.3
Transitivity = 0.2
Betweenness = 79.3



Small-World Network

Generated by a Watts–Strogatz model.

- Low node degree \Rightarrow “Six degrees of separation”
- Degree follow a Poisson distribution
- Low Transitivity than random
- Higher betweenness than random

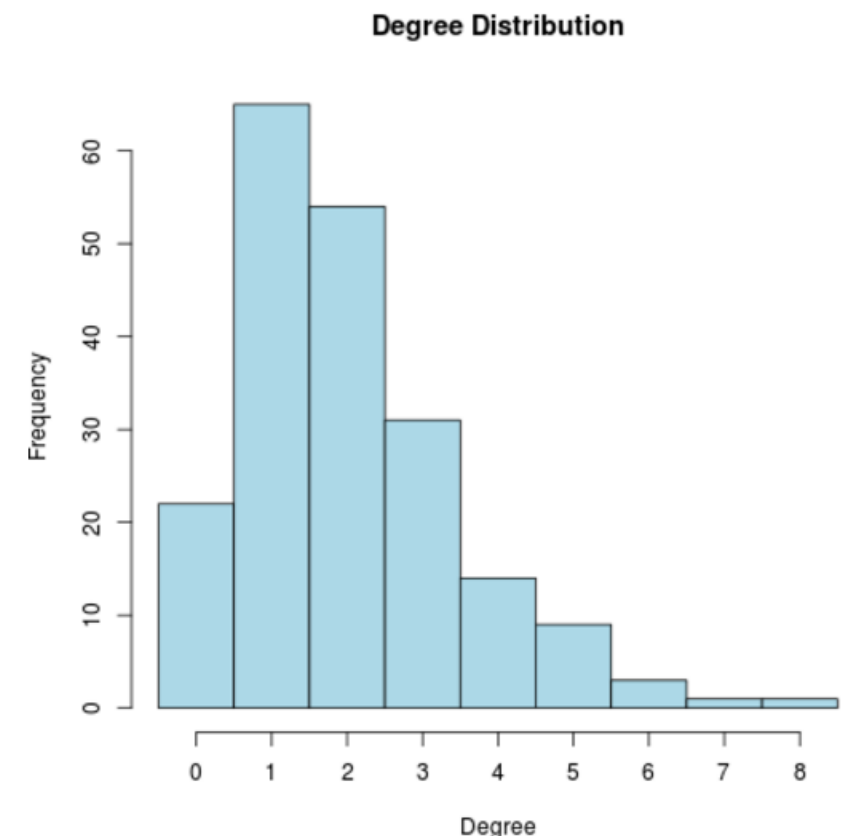
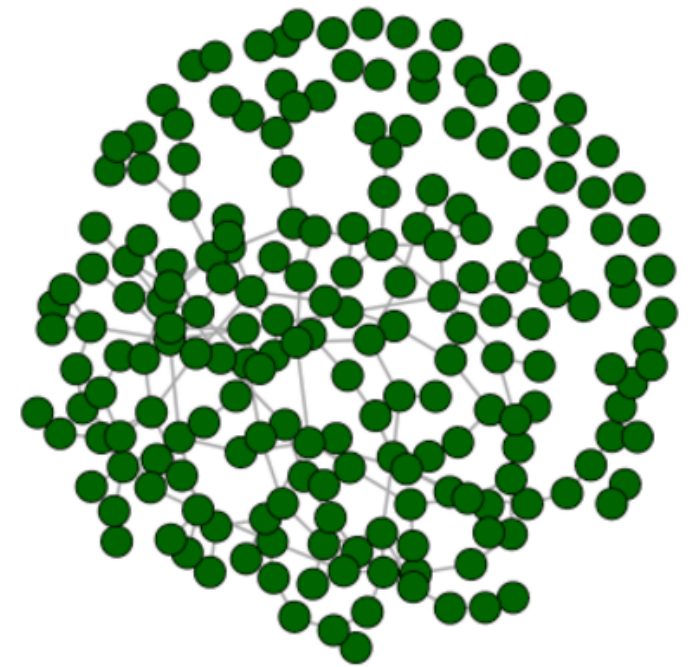
$$p(k) = \frac{\lambda^k e^{-\lambda}}{k!}$$

λ = the average value of the distribution
 k = number of observed events

Degree = 2

Transitivity = 0.01

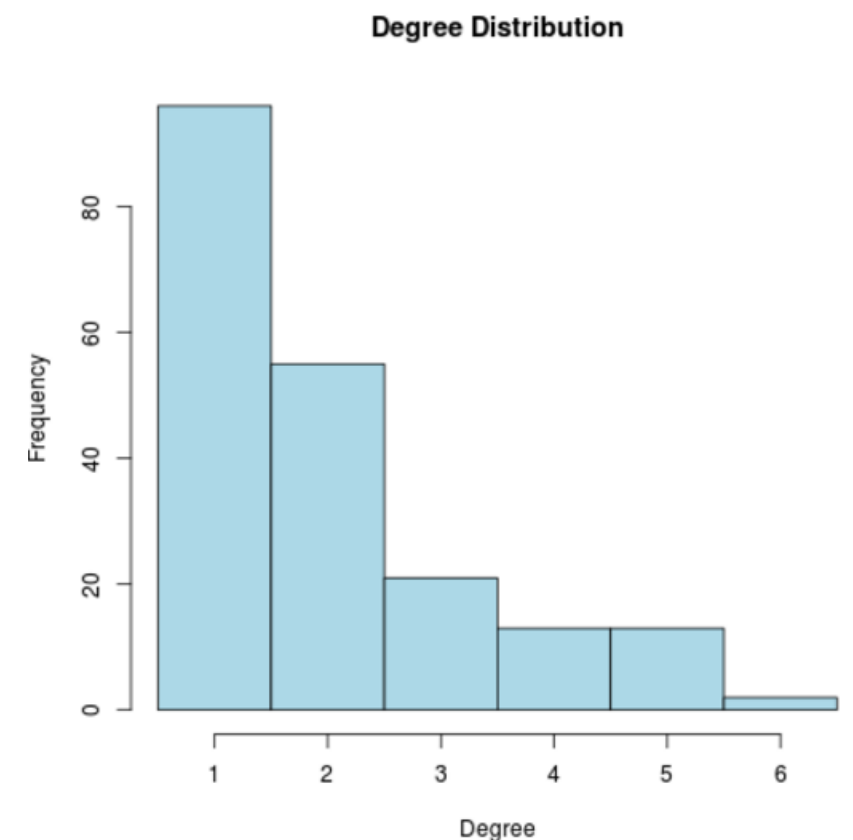
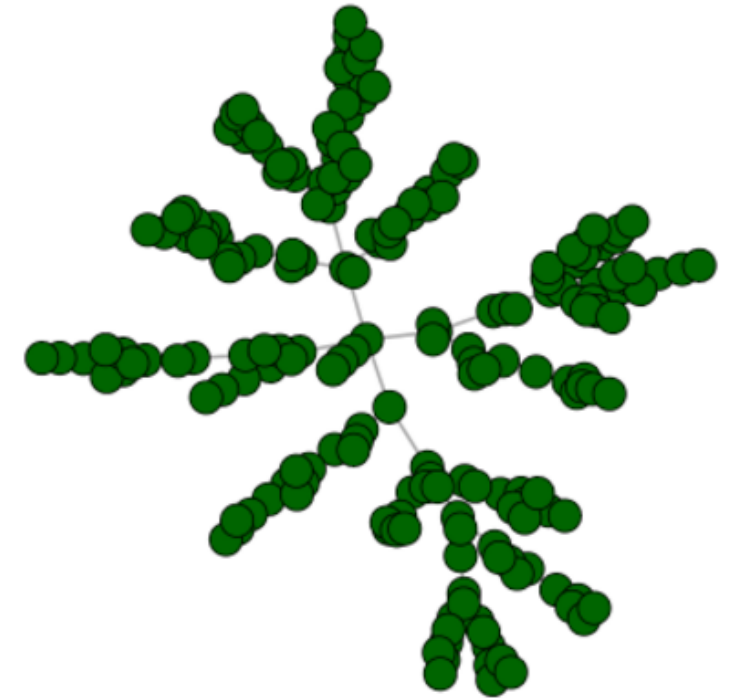
Betweenness = 394.9



Scale-Free Network

Generated by the Barabasi-Albert model.

- Smallest degree
- Degree follow a Power Law distribution
- Lowest Transitivity
- Highest Betweenness



$$p(k) = Ax^{-k}$$

x = is a constant
 k = number of observed events

Degree = 2

Transitivity = 0

Betweenness = 753.4

Biological Network

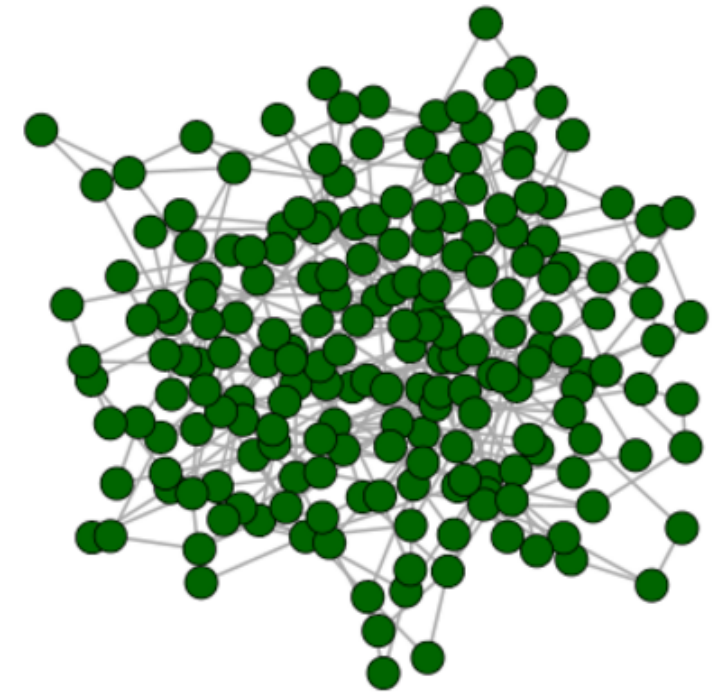
Similar to Small-World and Scale-Free networks

- Small degree
- Average path length proportional to $\ln(\ln(\#nodes))$
- Transitivity high than Small-World and Scale Free
- Betweenness lower than Small-World and Scale Free

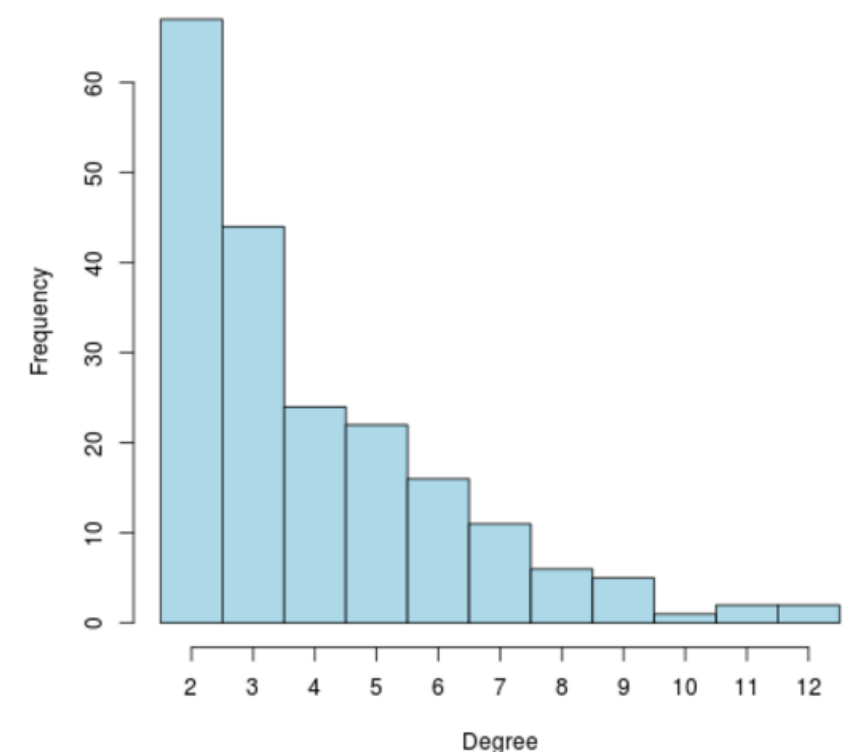
Degree = 4.0

Transitivity = 0.04

Betweenness = 290.4

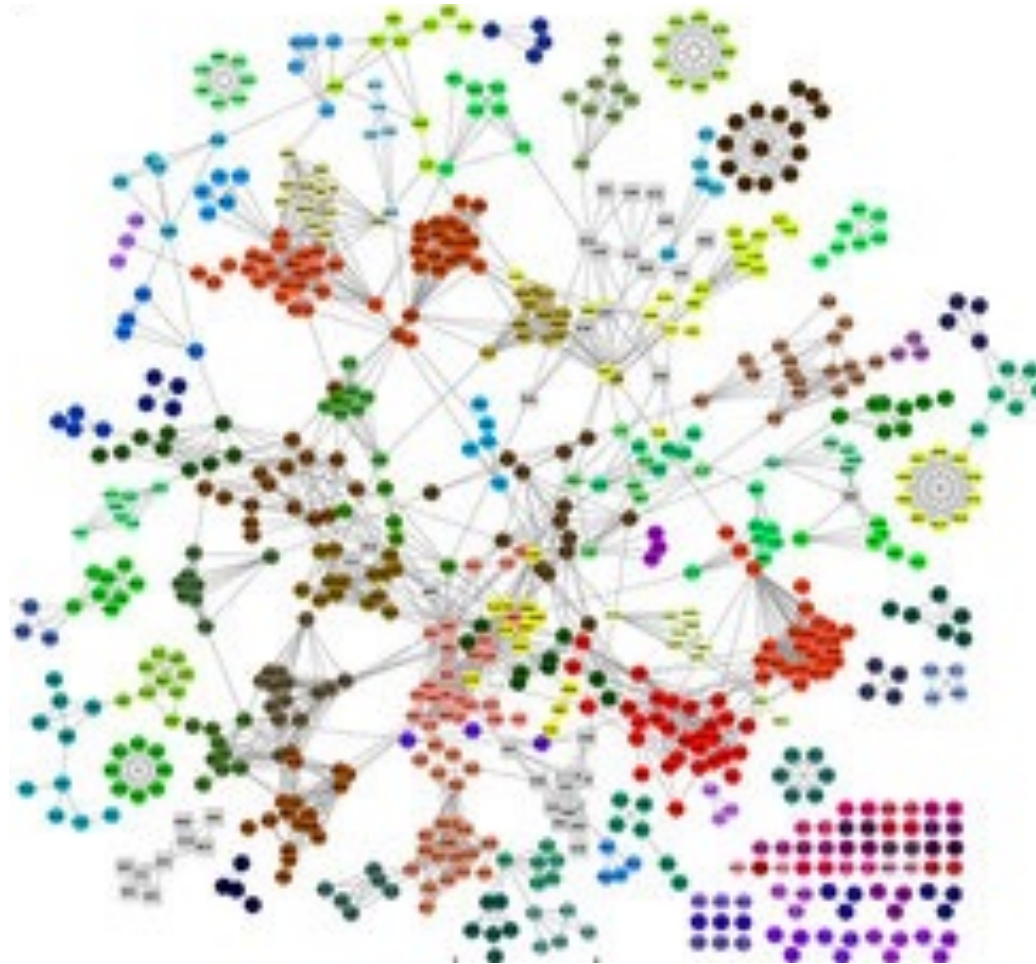


Degree Distribution



Community or Cluster

One of the main feature of the biological network is the **presence of communities or clusters**.



Gaiter, Scientific Reports 2015

Clusters are important to detect similarity between nodes (genes, diseases, etc) in the same cluster.

Network Robustness

Robustness, the ability to withstand failures and perturbations. It is a critical attribute of many complex systems including biological networks.

Robustness is tested removing nodes and checking if connections between the remaining nodes are conserved. This is possible because may exist alternative paths between two distinct nodes.

Biological networks persists despite the environmental noise, mutations etc.

Telecommunication networks resist to the attack of hackers and hardware failure

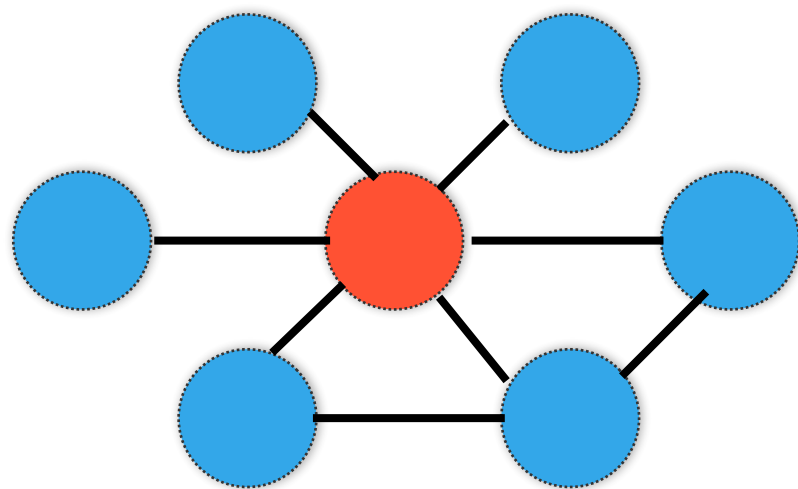
Network Perturbation

For **random networks the effect** of removing a single node is **on average the same**.

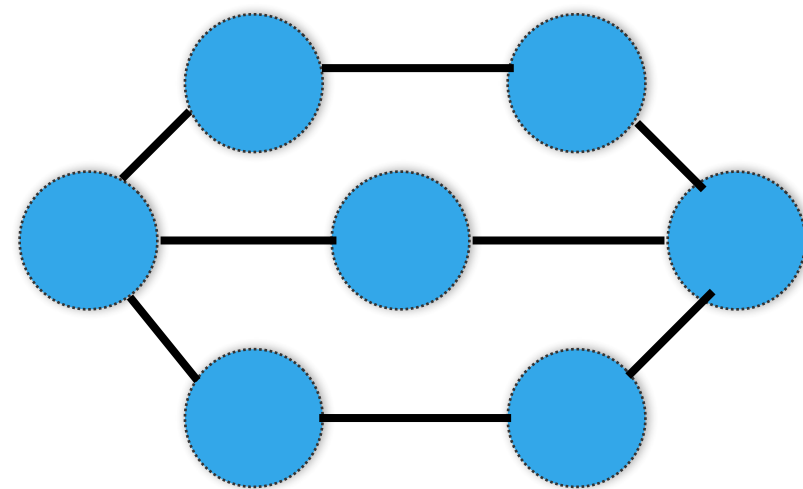
Biological networks are characterized by a small fraction of nodes with high degree (**hubs**)

An **attack that aims to a hub has strong effect** on the connectivity of the network.

In normal situation we assume that **attacks are random**. Thus, on average, an attack should have smaller effect on Biological Network.



Biological network

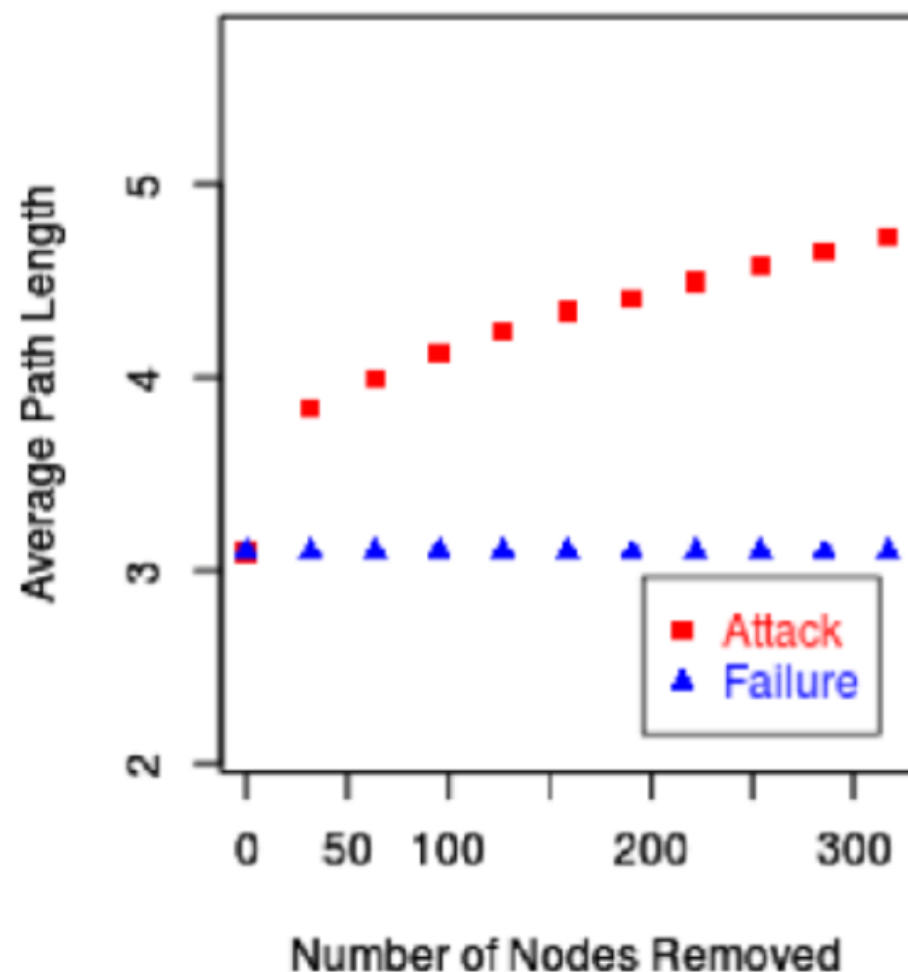


Random network

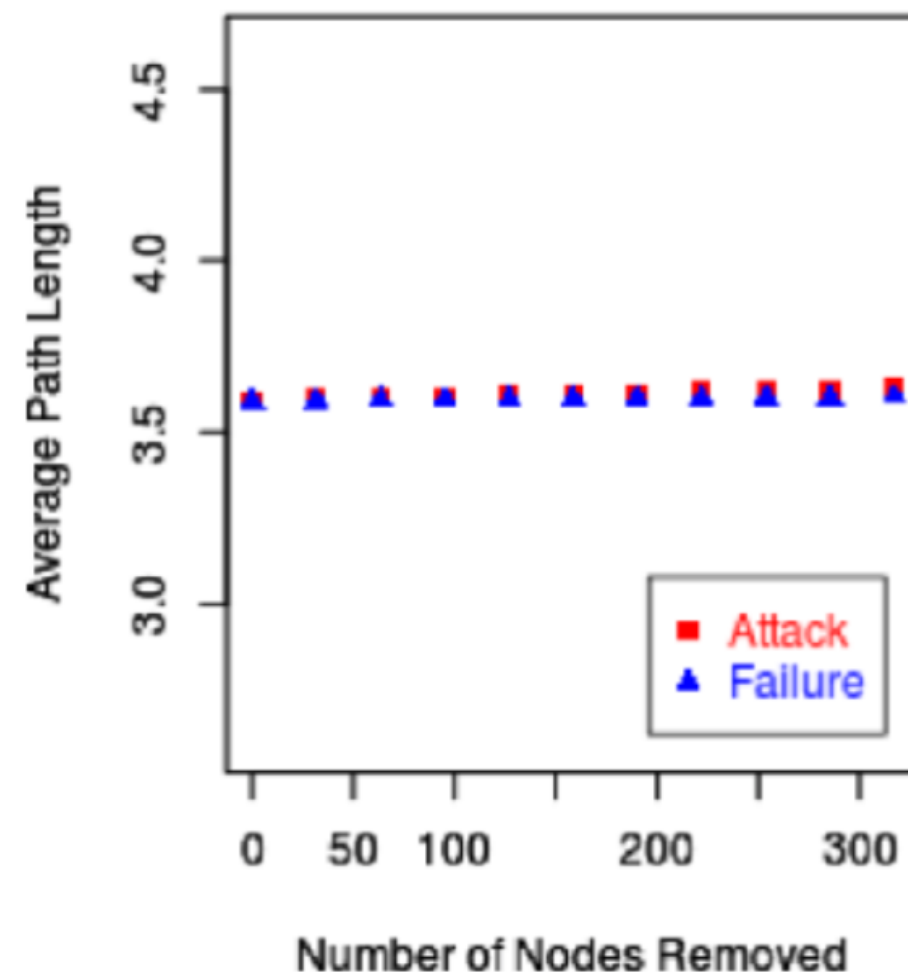
Failures and Attacks

The **resilience of scale free networks to failures** comes at the price of high **vulnerability to targeted attacks**

Homo Sapiens



Random Network



Python NetworkX

NetworkX is a Python package for the **creation, manipulation, and study** of the structure, dynamics, and functions of **complex networks**.

```
>>> import networkx as nx
```

```
>>> G = nx.Graph()
```

```
>>> G.add_node(1)
```

```
>>> G.add_nodes_from([2, 3]) # add list of nodes
```

```
>>> G.add_edge(1, 2)
```

```
>>> G.add_edges_from([(1, 2), (1, 3)]) # add list of edges
```

```
>>> G.number_of_nodes()
```

```
3
```

```
>>> G.number_of_edges()
```

```
2
```


Königsberg Graph

NetworkX is a Python package for the **creation, manipulation, and study** of the structure, dynamics, and functions of **complex networks**.

```
>>> import networkx as nx
>>> M = nx.MultiGraph()

>>> M.add_edges_from([(1, 2, {"name": "A"}),
...                   (1, 2, {"name": "B"}), (1, 3, {"name": "C"}),
...                   (1, 3, {"name": "D"}), (1, 4, {"name": "E"}),
...                   (3, 4, {"name": "F"}), (2, 4, {"name": "G"})])

>>> M = M.degree(1)
```

Network generators

Networkx has function that generate standard network types

```
>>> import networkx as nx  
>>> import matplotlib as plt
```

```
>>> er = nx.erdos_renyi_graph(100, 0.15)  
>>> ws = nx.watts_strogatz_graph(30, 3, 0.1)  
>>> ba = nx.barabasi_albert_graph(100, 5)
```

```
>>> nx.draw(ba)  
>>> plt.show()
```

BioGRID

The **Biological General Repository for Interaction Datasets** (BioGRID) is a curated biological database of protein-protein interactions, genetic interactions, chemical interactions, and post-translational modifications

The screenshot shows the BioGRID 4.2 homepage. At the top is a navigation bar with links: home, help, wiki, projects, tools, contribute, stats, downloads, partners, about us, and a Twitter icon. The main header area has a dark red background with the BioGRID 4.2 logo and a welcome message: "Welcome to our Database of Protein, Genetic and Chemical Interactions". Below this, a paragraph describes the database: "BioGRID is a biomedical interaction repository with data compiled through comprehensive curation efforts. Our current index is version 4.2.191 and searches 75,760 publications for 1,992,321 protein and genetic interactions, 29,093 chemical interactions and 959,750 post translational modifications from major model organism species. All data are freely provided via our search index and available for download in many standardized formats." To the right of the welcome message is a search box titled "Search BioGRID:" with a dropdown menu set to "By Protein/Gene". Below the search box is a text input field "Search by Protein/Gene Identifiers ...", a dropdown menu "All Organisms", and a "Submit Identifier Search Q" button. At the bottom of the search box are three icons: a magnifying glass for "Advanced Search", a flag for "Helpful Search Tips", and a star for "Featured Datasets". Below the search box are two buttons: "BioGRID Statistics" with a bar chart icon and "Latest Downloads" with a download icon. A yellow banner across the middle of the page reads "BioGRID COVID-19 Coronavirus Curation Project" and "Search BioGRID for SARS-CoV-2 Protein Interactions | Download SARS-CoV-2 and Coronavirus-Related Interactions". Below the banner is a section titled "Related Resources" with a sub-section "BioGRID Themed Curation Projects" which describes themed curation projects and includes a "Learn more" link. To the right of the "Related Resources" section is a "Partners" section with logos for NIH, ORIP (Office of Research Infrastructure Programs), CIHR IRSC, Mount Sinai Hospital, Princeton University, and Université de Montréal.

BioGRID 4.2 home help wiki projects tools contribute stats downloads partners about us

Welcome to our Database of Protein, Genetic and Chemical Interactions

BioGRID is a biomedical interaction repository with data compiled through comprehensive curation efforts. Our current index is version **4.2.191** and searches **75,760** publications for **1,992,321** protein and genetic interactions, **29,093** chemical interactions and **959,750** post translational modifications from major model organism species. All data are **freely** provided via our search index and available for download in many standardized formats.

BioGRID Statistics **Latest Downloads**

Search BioGRID: By Protein/Gene

Search by Protein/Gene Identifiers ...

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Advanced Search Helpful Search Tips Featured Datasets

BioGRID COVID-19 Coronavirus Curation Project

Search BioGRID for **SARS-CoV-2 Protein Interactions** | Download SARS-CoV-2 and Coronavirus-Related Interactions

Related Resources

BioGRID Themed Curation Projects

BioGRID themed curation projects focus on specific biological processes with disease relevance. Core genes/proteins central to the process are assembled with expert input and relevant publications curated for biological interactions. Themed curation projects are updated monthly and additional projects are generated on a regular basis.

[Learn more](#)

Partners

NIH ORIP OFFICE OF RESEARCH INFRASTRUCTURE PROGRAMS CIHR IRSC

Mount Sinai Hospital PRINCETON UNIVERSITY Université de Montréal

<https://thebiogrid.org/>

Exercise

Generate the three types of network (random, "small world" and "scale free") and calculate the distribution of the degree, betweenness and clustering.

From BioGRID download the Yeast interactome and analyze it with networkx importing only a list of unique interactions from the BIOGRID repository:

- How many components are present?
- What is the gene with highest degree?
- What is the the average values of degrees, betweenness and clustering?