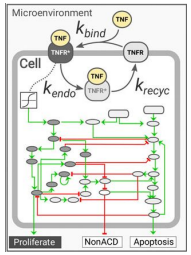
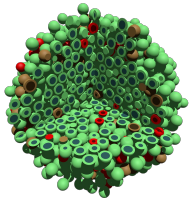
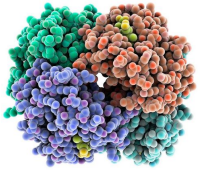
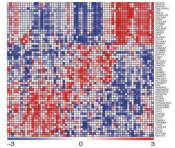




De las redes intracelulares a las simulaciones de sistemas multicelulares





Profesor: Dr. Miguel Ponce de León (miguel.ponce@bs.es) - BSC

Coordinador: Dr. Flavio Pazos (flavio.pazos@gmail.com) - IIBCE/IP

Apoyan:

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Tema 3

Fundamentos de teoría de grafos y redes complejas (Parte I)

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Graph Theory I & II

- Why use network representation?
- A bit of history
- Basic definitions and graph types
- Graph representations
- Graph traversing and shortest path problems

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Levels of description of a system

- **Structure**
  - Components + interactions
- **Dynamics**
  - Steady states, Bi-stability
  - Oscillations, Chaos, etc
- **Control (regulation)**
  - Homeostasis (robustness)
  - Positive or Negative Feedback loops

Complexity due to the large number of parameters and non-linear interactions!

"... With four parameters I can fit an elephant, and with five I can make him wiggle his trunk..."

John von Neumann (~1953)

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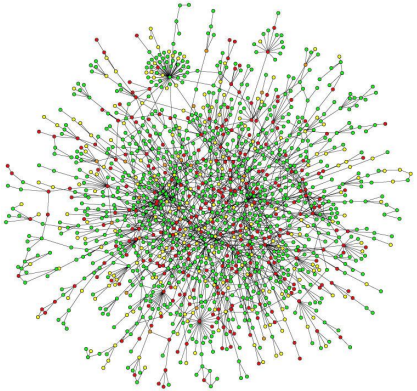
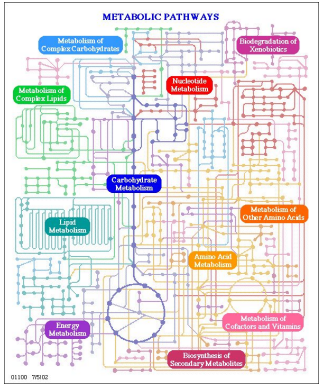
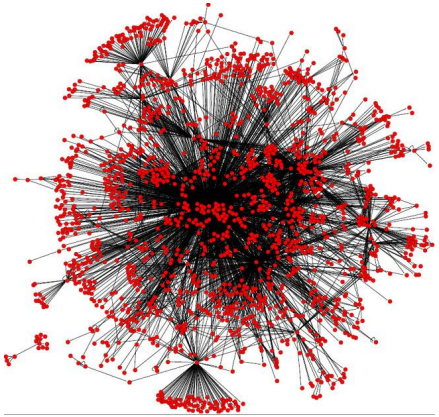
Networks are everywhere!



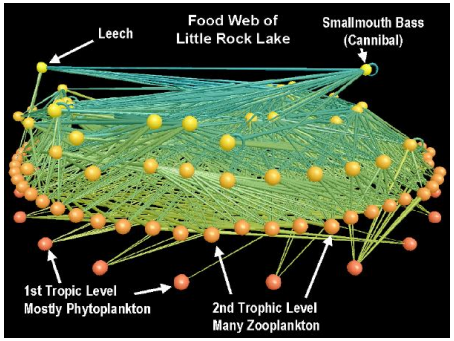
PPi networks



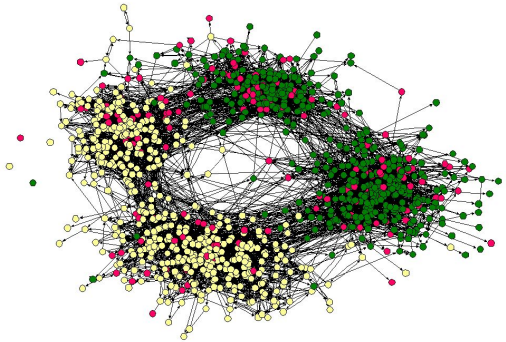
Metabolic networks



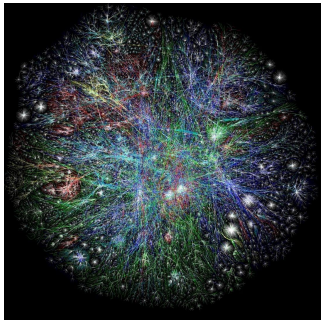
Regulatory networks



Ecological networks



Social networks



Technological networks

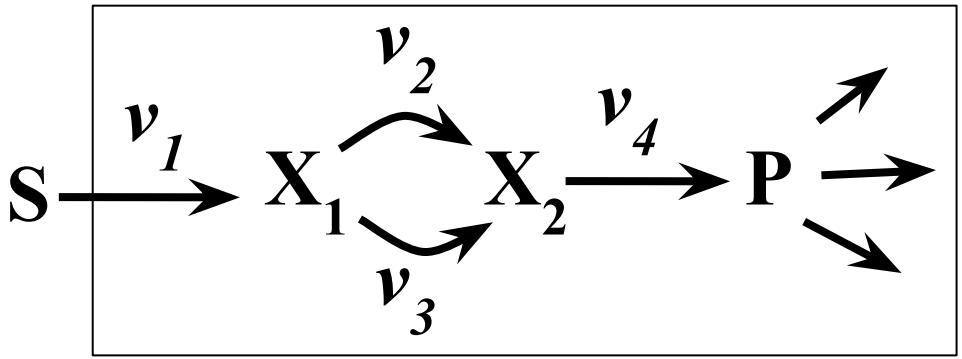
Properties of Models: behavior

Structure: relation between variables and parameters

Dynamic: time-evolution of systems variable

Causes:

- *External:* influences from the environment (input)
- *Internal:* processes within the system, noise, etc.



Structure

$$\begin{bmatrix} 1 & -1 & -1 & 0 \\ 0 & 1 & 1 & -1 \end{bmatrix} \begin{bmatrix} v_1 \\ v_2 \\ v_3 \\ v_4 \end{bmatrix} = \begin{bmatrix} \frac{d[A]}{dt} \\ \frac{d[B]}{dt} \end{bmatrix}$$

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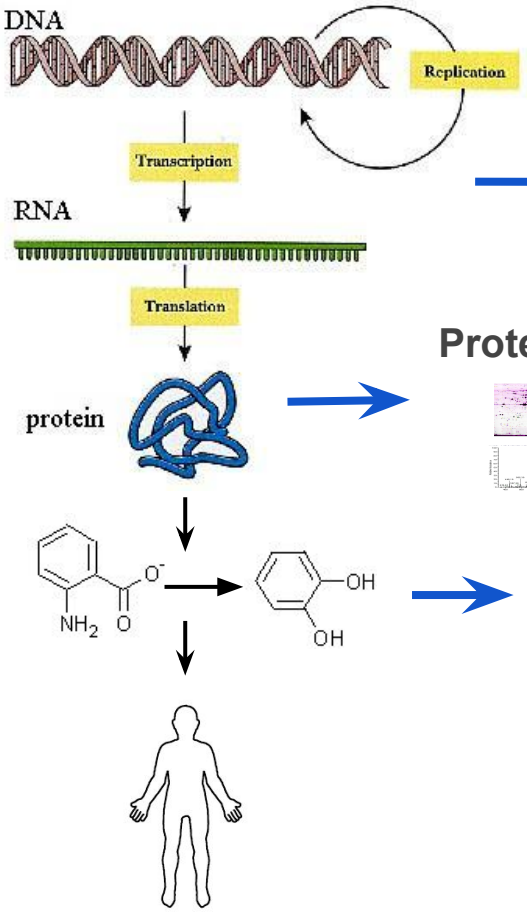
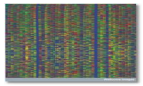
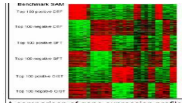
From omics to network reconstruction



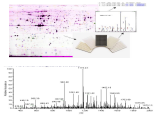
Genomics



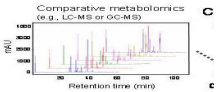
Transcriptomics



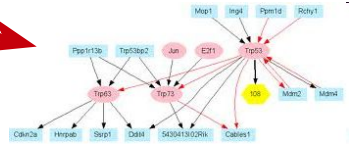
Proteomics



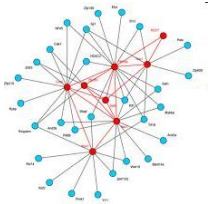
Metabolomics



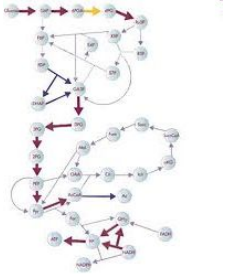
Gene regulation nets

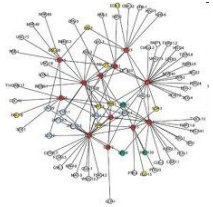


Protein nets (interaction, fosforilation, signaling)



Metabolic nets





Genotype nets, phenotipic nets, disease-related nets, …

What is a Network?

- **Network** = graph
- Informally a graph is a set of **nodes** joined by a set of **lines** or **arrows**.

What is a Network?

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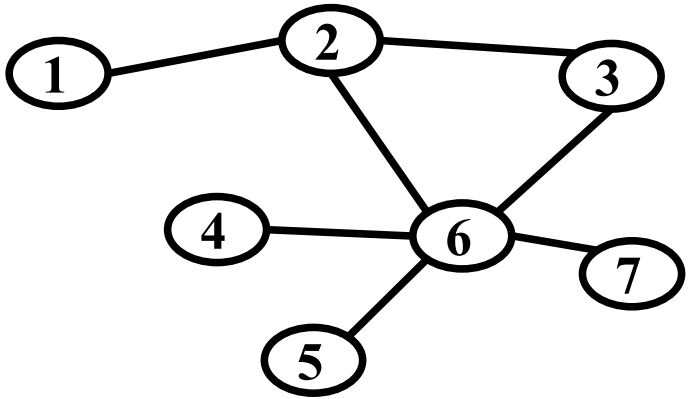

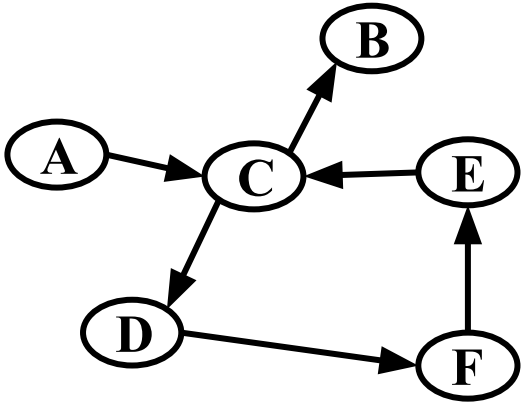

Graph-based representations

- Representing a problem as a graph can provide a different point of view
- Representing a problem as a graph can make a problem much simpler
  - More accurately, it can provide the appropriate tools for solving the problem

What is network theory?

- ***Network theory*** provides a set of techniques for analyzing graphs
- ***Complex systems network theory*** provides techniques for represent and analyze any system of interacting agents, which can be represented as a network
- Applying network theory to a system means using a graph-theoretic representation

What makes a problem graph-like?

- There are two components to a graph
  - **Nodes** and **edges**
- In graph-like problems, these components have natural correspondences to problem elements
  - **Entities** are nodes and **interactions** between entities are edges
- Most complex systems are graph-like

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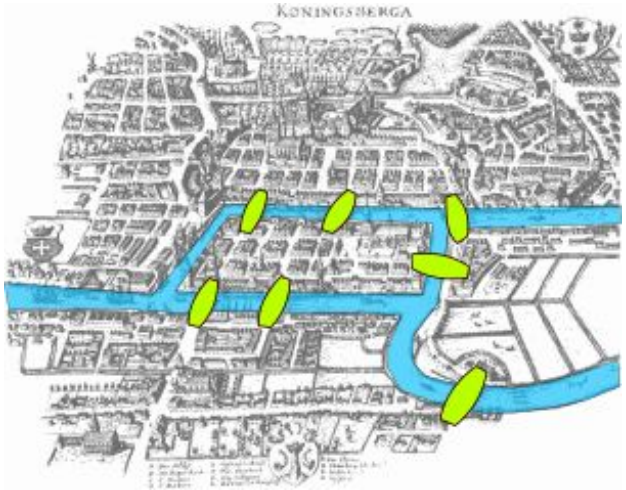
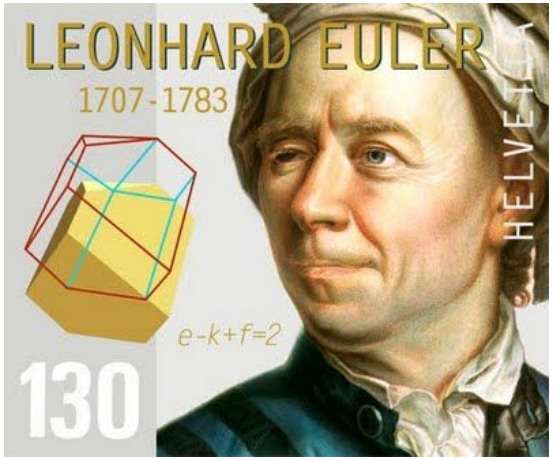
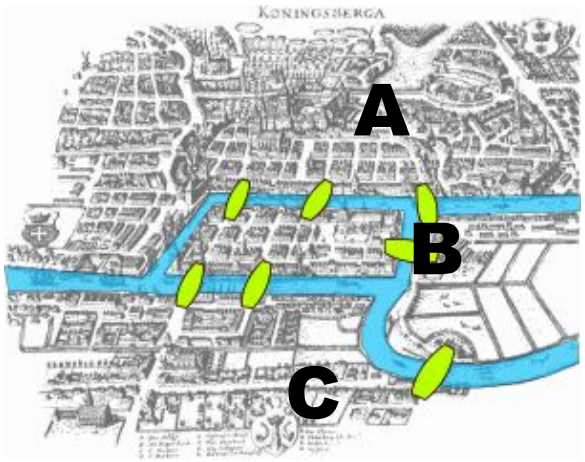
Introduction to graph theory: history

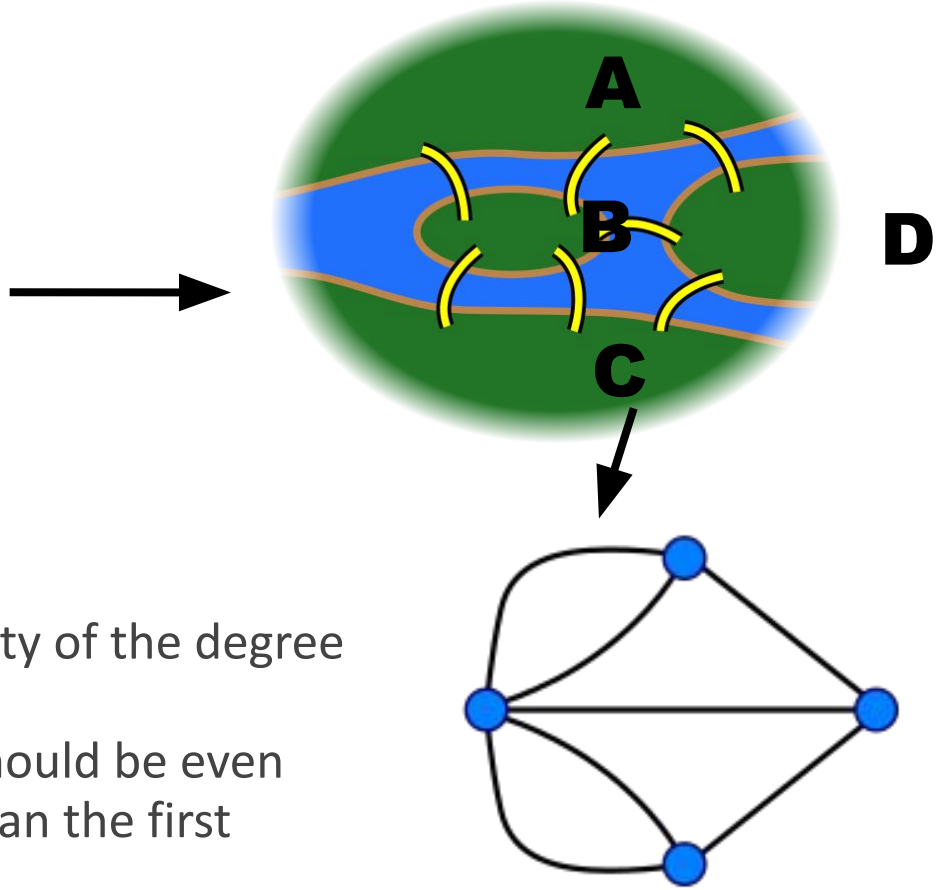
- **Graph** theory was born around ~1735
- Developed to solve Bridges of Konigsberg problem:
  - traverse through the 7 bridges of the city without crossing a bridge twice and go back to the origin





Introduction to graph theory: history



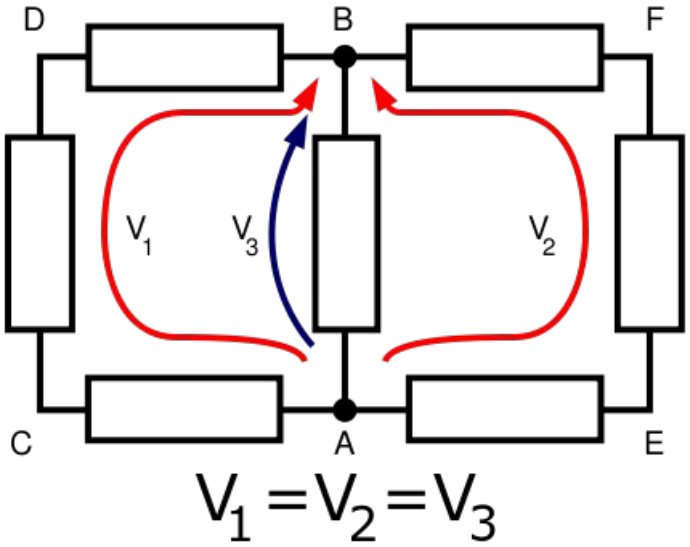


- The solution is based on the parity of the degree of each node
- Degree of intermediate nodes should be even
- The last node is the same one than the first

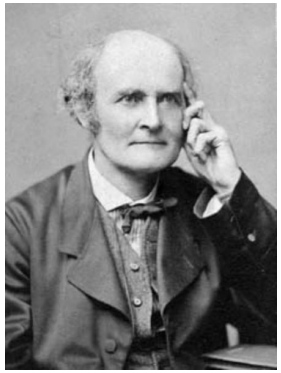
Introduction to graph theory: history

Trees in Electric Circuits

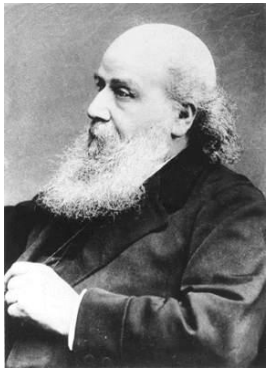
Gustav Kirchhoff



Introduction to graph theory: history

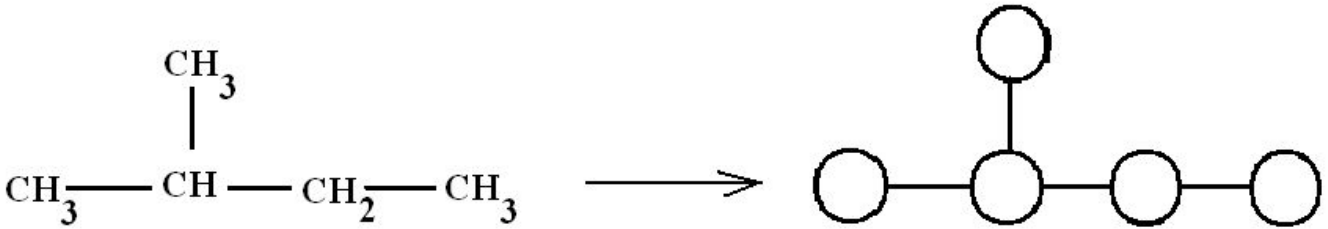


Arthur Cayley



James J. Sylvester

George Polya



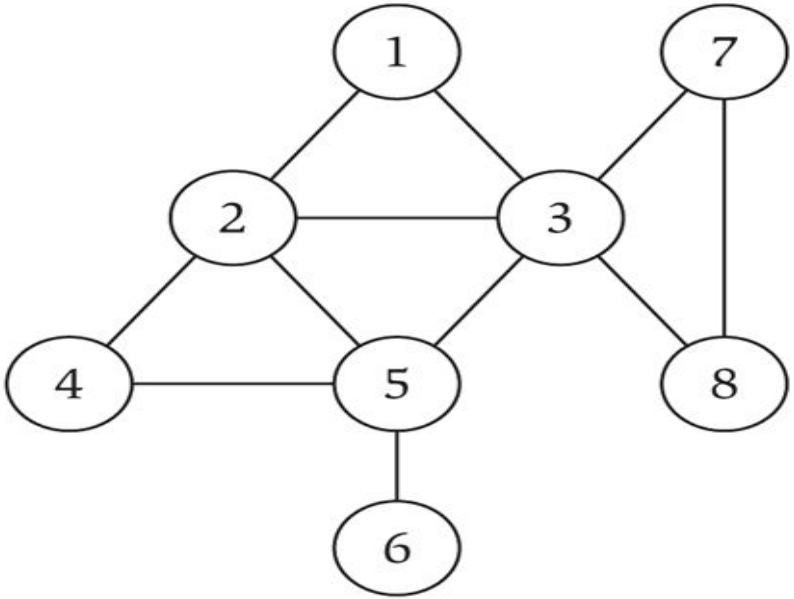
Graph theory: definitions

- **Graph** → mathematical object consisting of a set of:
  - V = **nodes** (vertices, points).
  - E = **edges** (links, arcs) between pairs of nodes.
  - Denoted by $G = (V, E)$.
  - Captures pairwise relationship between objects.
  - **Graph size** parameters: $n = |V|$, $m = |E|$.

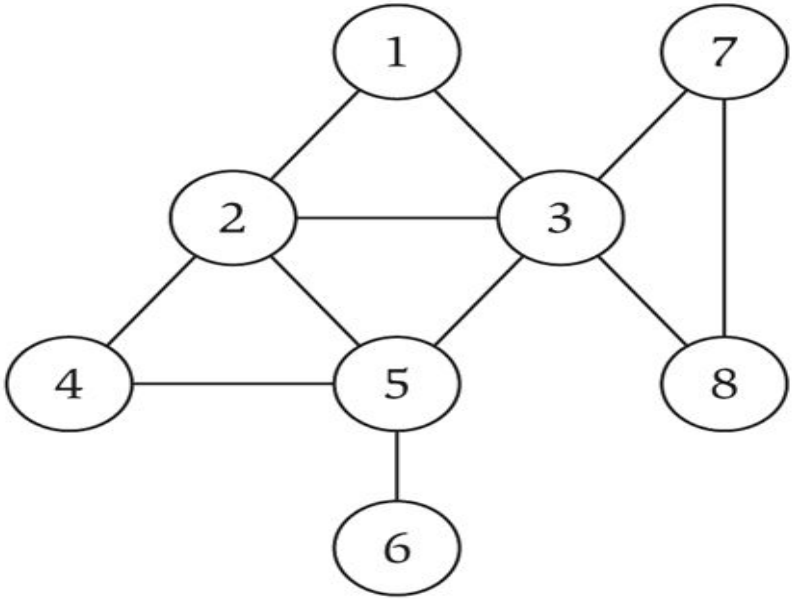
Graph theory: definitions

- **Vertex**
  - Basic Element
  - Drawn as a node or a dot.
  - Vertex set of G is usually denoted by **V(G)**, or $\mathbf{V_G}$
- **Edge**
  - A set of two elements
  - Drawn as a line connecting two vertices, called end vertices, or endpoints.
  - The edge set of G is usually denoted by **E(G)**, or $\mathbf{E_G}$

Graph theory: example



Graph theory: example



- $V = \{ 1, 2, 3, 4, 5, 6, 7, 8 \}$
- $E = \{\{1,2\},\{1,3\},\{2,3\},\{2,4\},\{2,5\},\{3,5\},\{3,7\},\{3,8\},\{4,5\},\{5,6\}\}$
- $n = 8$
- $m = 11$

Graph theory: definitions

Set Notation

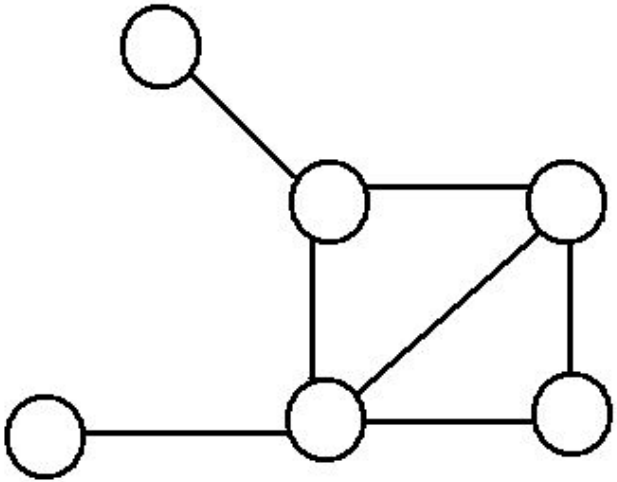
- $\mathbf{A = \{1, 2, 3\}}$ → Set definition (by extension)
- $\mathbf{A = \{x \,/\, x \in N, 0 < x < 4\}}$ → Set definition (comprehension)
- $\mathbf{A = B}$ → equal sets
- $\mathbf{A \cup B}$ → union of sets A and B
- $\mathbf{A \cap B}$ → intersection of sets A and B
- $\mathbf{A \subseteq B}$ → A is included in B
- $\boldsymbol{x} \in \mathbf{A}$ → x is an element of set A

Graph theory: definitions

- **For graph G(V,E):**
  - If edge e={u,v} ∈ E(G), we say that **u and v are adjacent** or **neigbors**
  - u and v are **incident** with e
  - u and v are end-vertices of e
  - An edge where the two end vertices are the same is called a **loop**, or a self-loop
- **Graph types:**
  - Simple or Undirected
  - Directed or Digraph
  - Mixed (some edges directed some undirected)
  - Weighted (weights on edges or nodes)

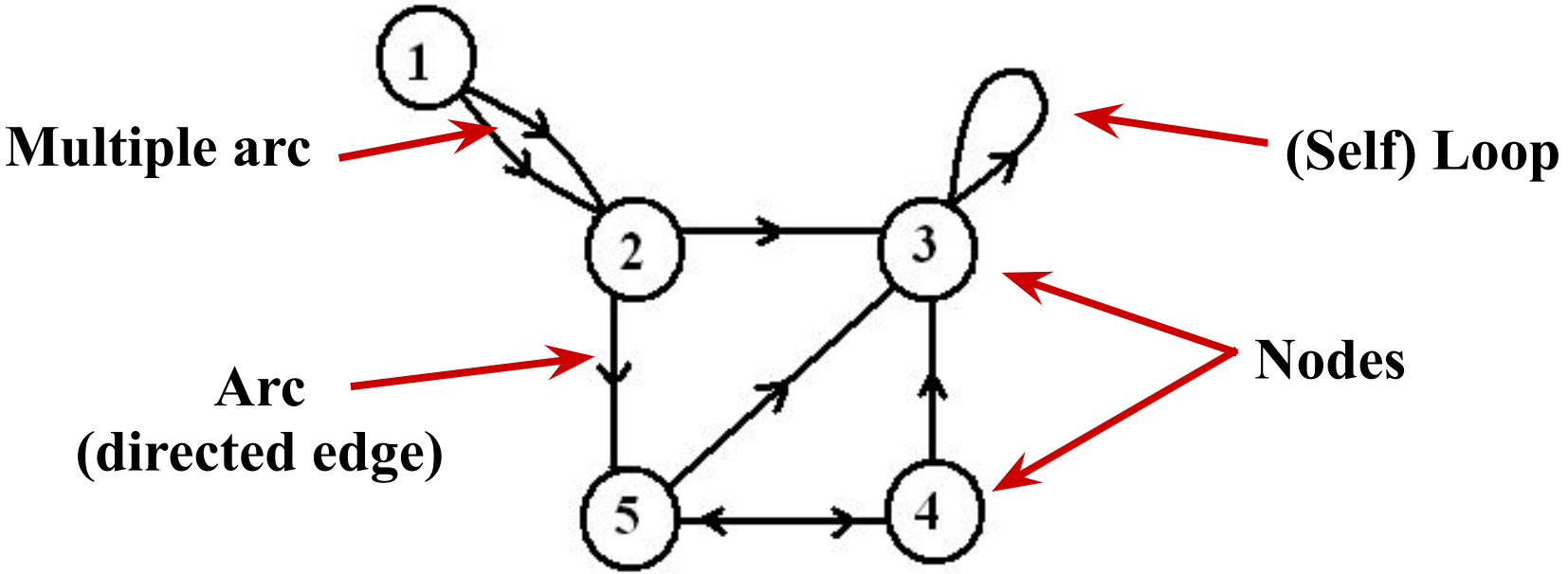
Simple Graphs

Simple graphs are graphs without multiple edges or self-loops.



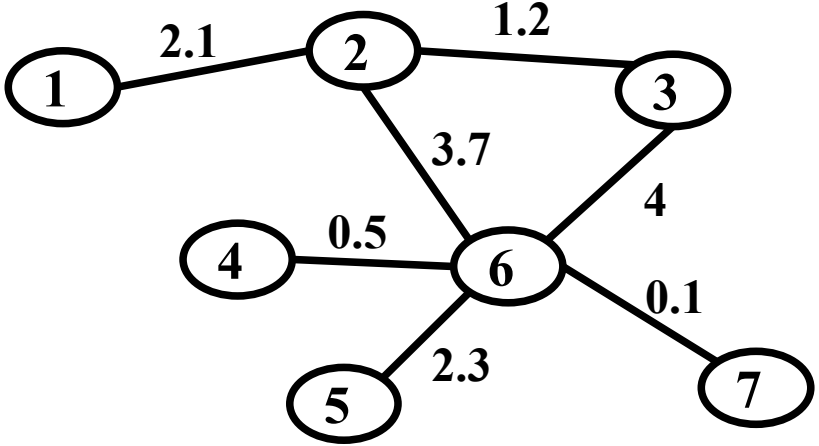
Directed Graph (digraph)

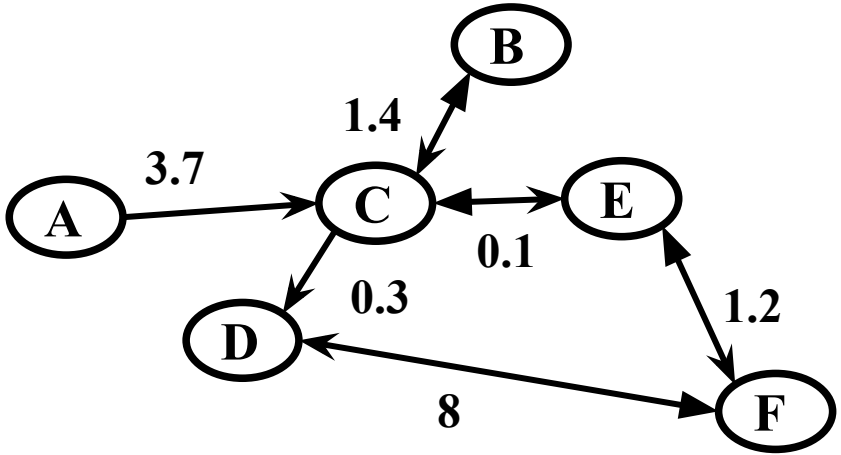
- Edges have **directions** (named arcs)
- An edge is an ordered pair of nodes



Weighted Graph: G = (V, E, w)

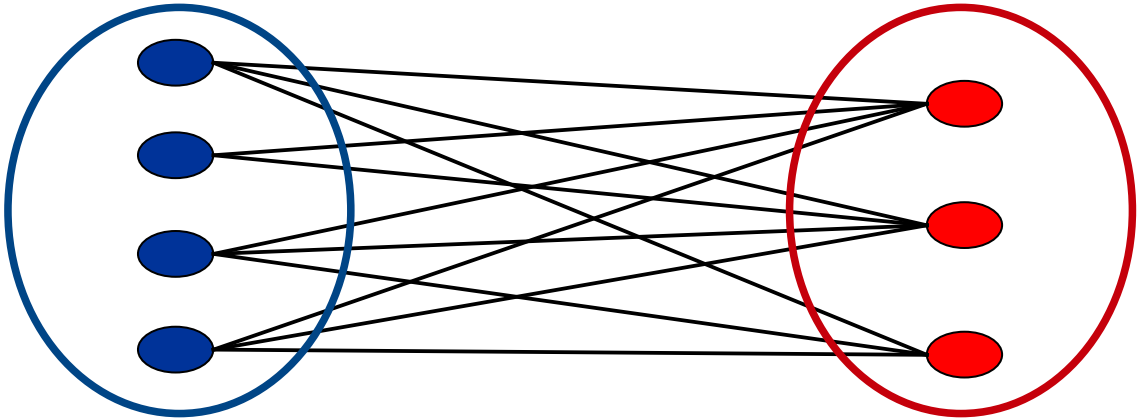
- Is a graph for which each edge has an associated ***weight***, usually given by a ***weight function*** *w:*
  - $E \rightarrow \mathbf{R}$ (*i.e.* each edge is assigned to a real values).





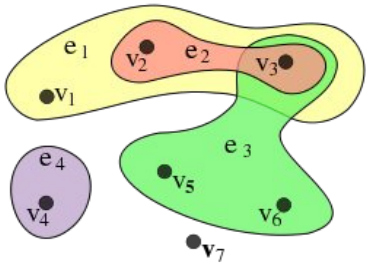
Bi-partite graphs

- **Def.** An undirected graph G = (V, E) is **bipartite** if the nodes can be colored red or blue such that every edge has one red and one blue end.
- **Applications:**
  - *Scheduling:* machines = red, jobs = blue.
  - *Metabolic networks:* metabolites = blue, enzymes = red.



Hypergrahs

- **Hypergraphs**: $E \subseteq 2^V$ (all subsets of elements of V)
  - Each edge (hyperedge) is a subset of vertices.
- **Example:**
  - $V = \{v_1, v_2, v_3, v_4, v_5, v_6, v_7\}$
  - $E = \{e_1, e_2, e_3, e_4\} = \{\{v_1, v_2, v_3\}, \{v_2, v_3\}, \{v_3, v_5, v_6\}, \{v_4\}\}$



- **Applications:**
  - Rarely used in network biology...
  - metabolic networks where several substrates react to build products.

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Structures and structural metrics

- **Graph structures** are used to isolate interesting or important sections of a network

- **Structural metrics** provide **measurements** of structural properties of a graph or network:

  - **Local metrics:** refer to a single node in a graph (*e.g.* degree)

  - **Global metrics:** refer to a whole graph (*e.g.* diameter)

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Structures and structural metrics

Graph structures are used to isolate interesting or important sections of a network

Structural metrics provide **measurements** of structural properties of a graph or network:

- **Local metrics:** refer to a single node in a graph (*e.g.* degree)
- **Global metrics:** refer to a whole graph (*e.g.* diameter)

Graph structures

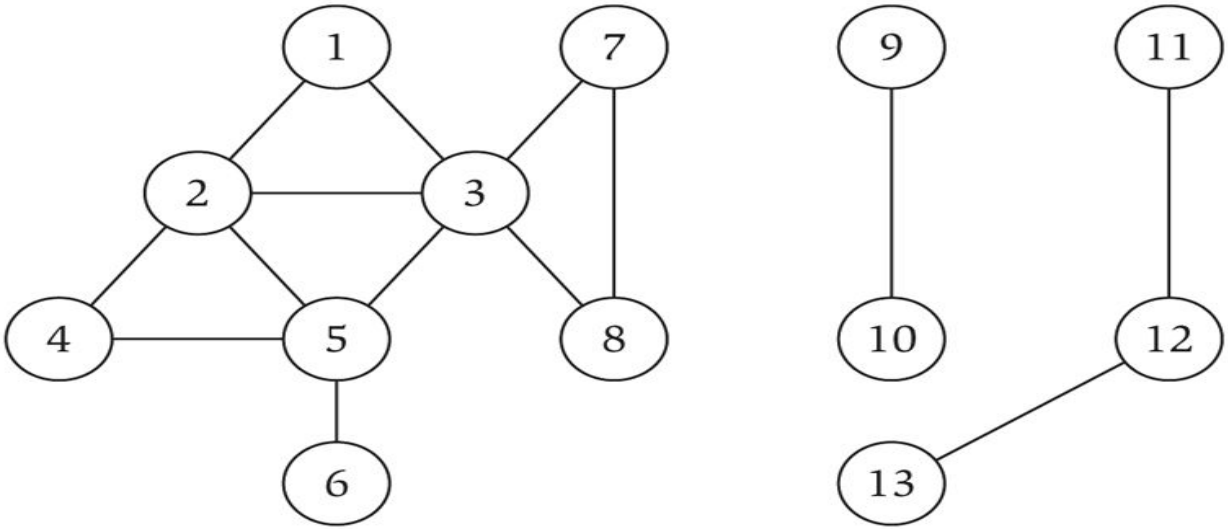
- Identify **interesting sections** of a graph
- Interesting because:
  - form a significant domain-specific structure
  - they significantly contribute to graph properties
- A subset of the nodes and edges in a graph that **possess certain characteristics**, or relate to each other in particular ways

Graph connectivity

- A graph is **connected** if
  - Any node can reach any other by following a sequence of edges
  - (**Or**) any two nodes are connected by a **path**.
- A directed graph is **strongly connected** if there is a **directed path** from any node to any other node.

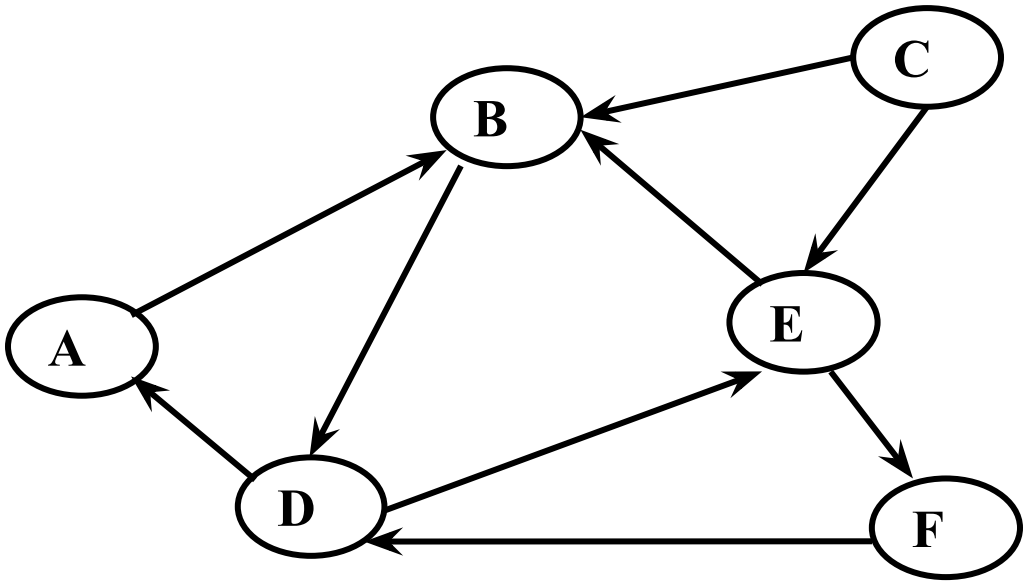
Connected Components

. Every disconnected graph can be split up into a number of **connected components.**



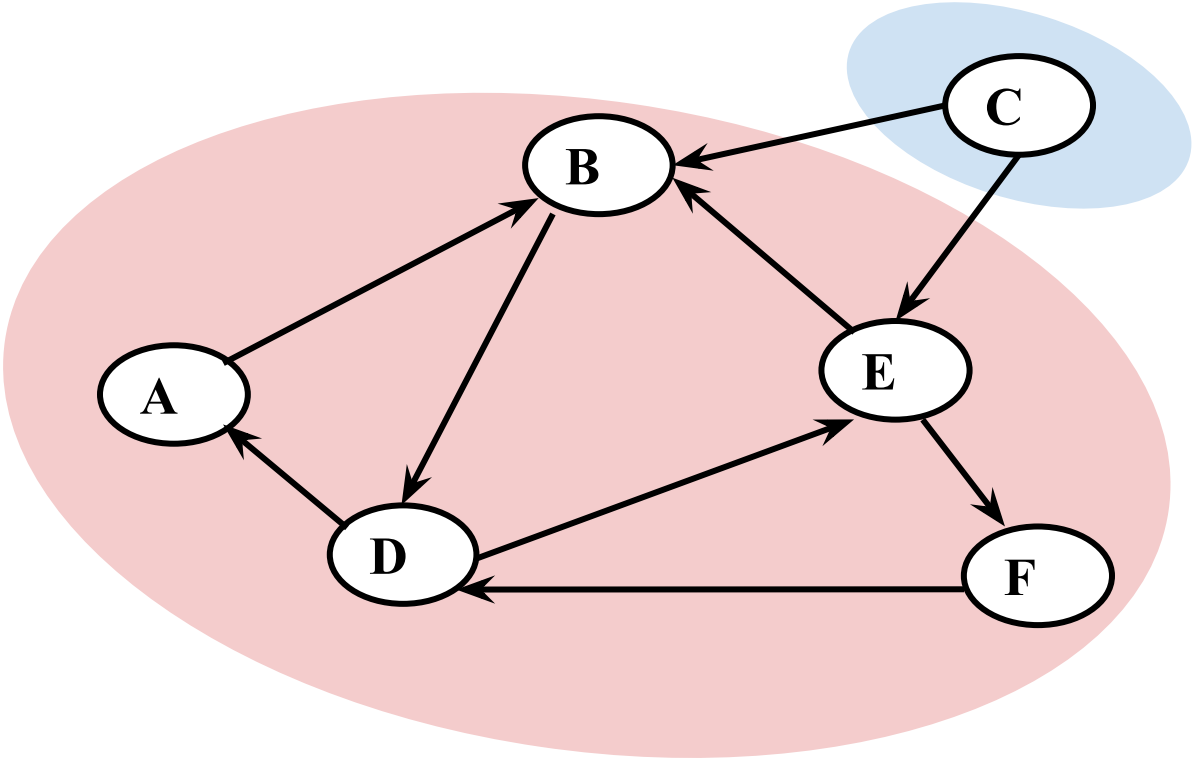
Strongly Connected Components

. How many **strongly connected components** are in the graph?



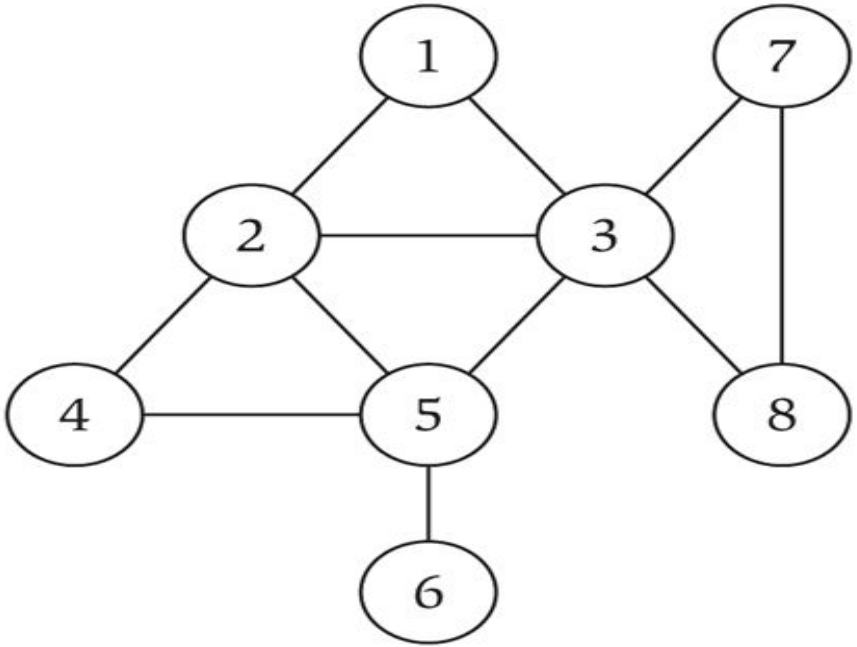
Strongly Connected Components

. How many **strongly connected components** are in the graph?



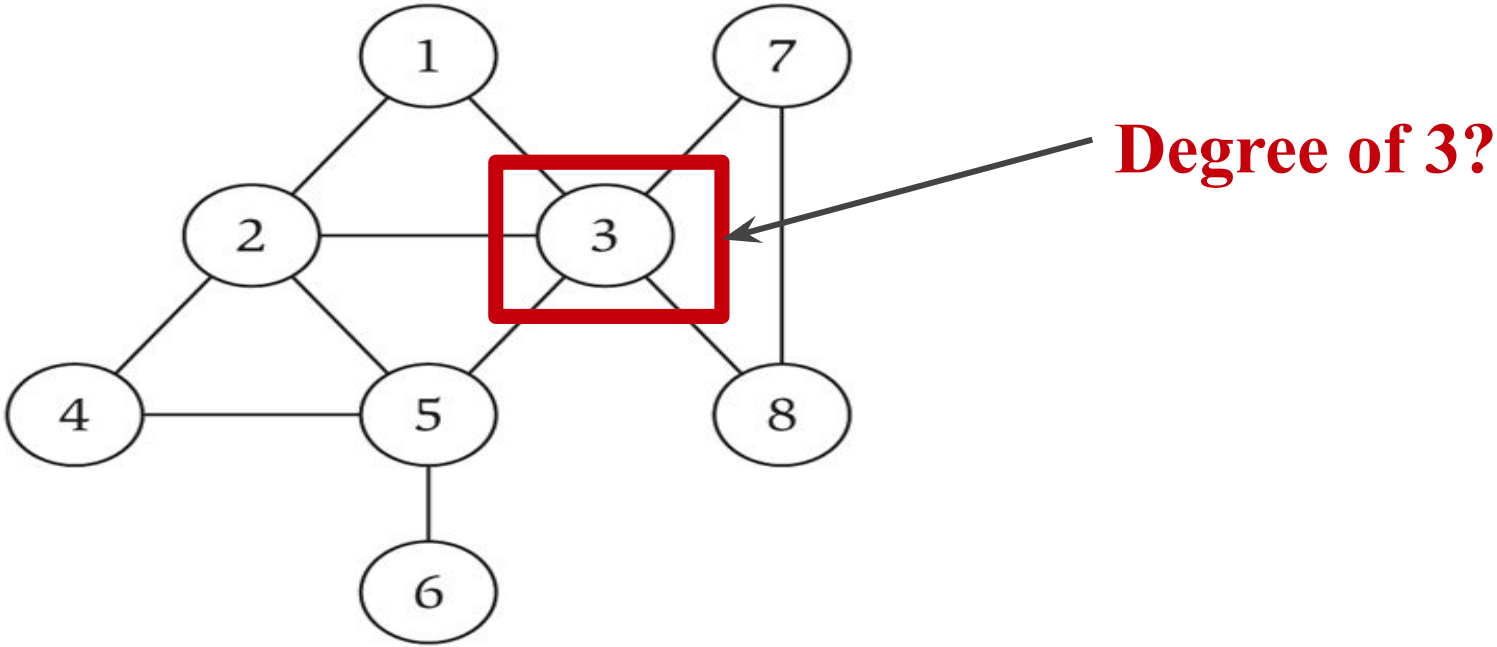
Degree of a node

- Number of edges incident on a node



Degree of a node

- Number of edges incident on a node



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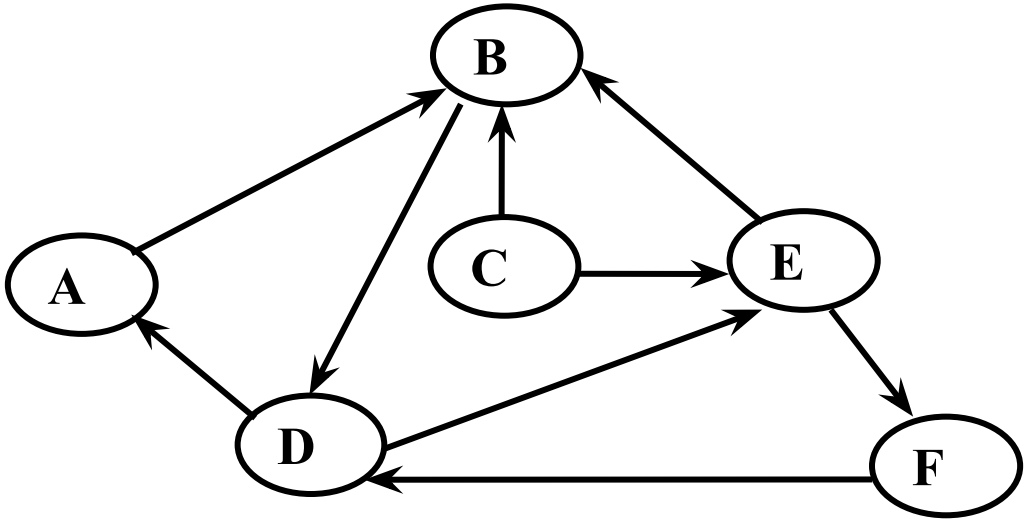
Degree of a node (Di-graph)

- **In-degree:** Number of edges entering
- **Out-degree:** Number of edges leaving
- Degree = indeg + outdeg



Examples

- In-degree(**A**) = 1
- Out-degree(**A**) = 1

- In-degree(**B**) = 3
- Out-degree(**B**) = 1

- In-degree(**E**) = ?
- Out-degree(**E**) = ?

Degree: simple facts

- If G is a graph with m edges, then
  - $\Sigma \deg(v) = 2m = 2\,|E\,|$
- If G is a digraph then
  - $\Sigma \text{ indeg}(v) = \Sigma \text{ outdeg}(v) = |E\,|$
- Number of Odd degree Nodes is even

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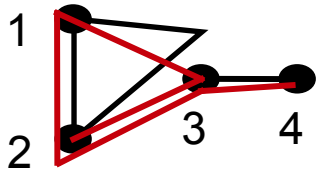
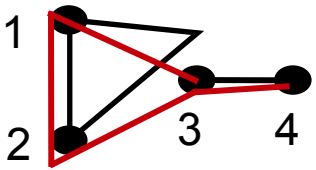
Path and walks

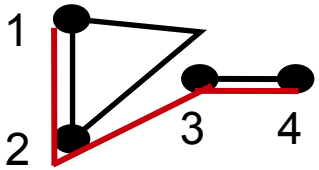
- **Def.** A **path** in an undirected graph G = (V, E) is a sequence P of nodes $v_1, v_2, \ldots, v_{L-1}, v_L$ where each
  - $(v_i, v_{i+1}) \in E$ for all $i = 1 \ldots L-1$
- (nodes can repeat, but edges do not.)
- **Def.** A **walk** is a path in which edges/nodes can be repeated.
- **Def.** A **path is simple** if all nodes are distinct.



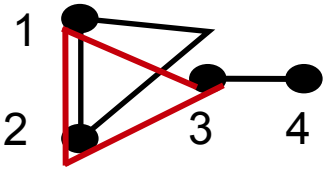
Walk:
{2,3}, {3,1}, {1,2}, {2,3}, {3,4}



Path:
{3,1}, {1,2}, {2,3}, {3,4}



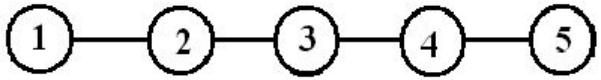
Simpl Path:
{1,2}, {2,3}, {3,4}



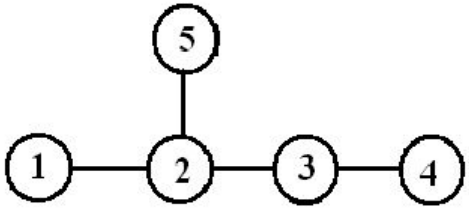
Cycle:
{3,1}, {1,2}, {2,3}

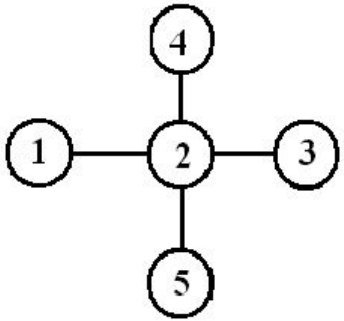
Trees

- Connected **Acyclic Graph**
- Two nodes have exactly one path between them
- **Examples:**



Path



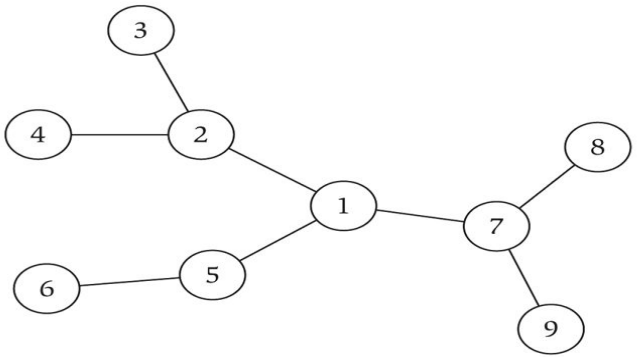


Star

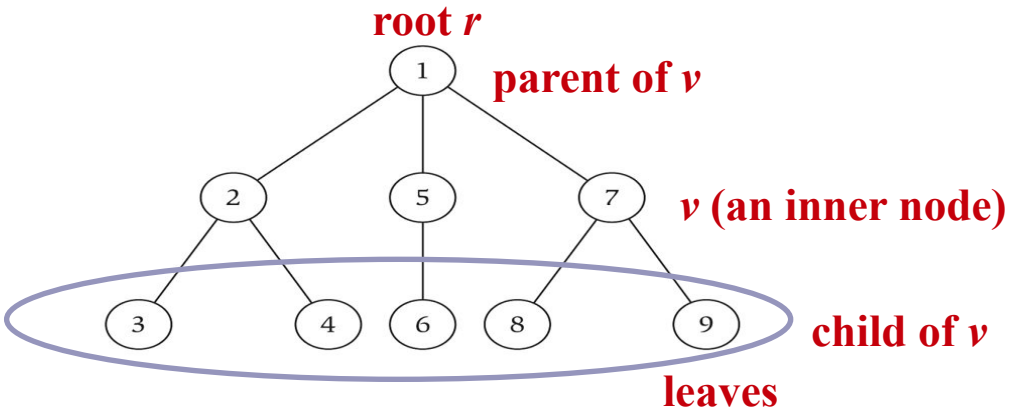
Trees and roots

- **Rooted tree.** Given a tree T, choose a root node r and orient each edge away from r.
- **Importance:** Models hierarchical structure.

a tree



the same tree, rooted at 1



Statistical properties of networks: degree distribution

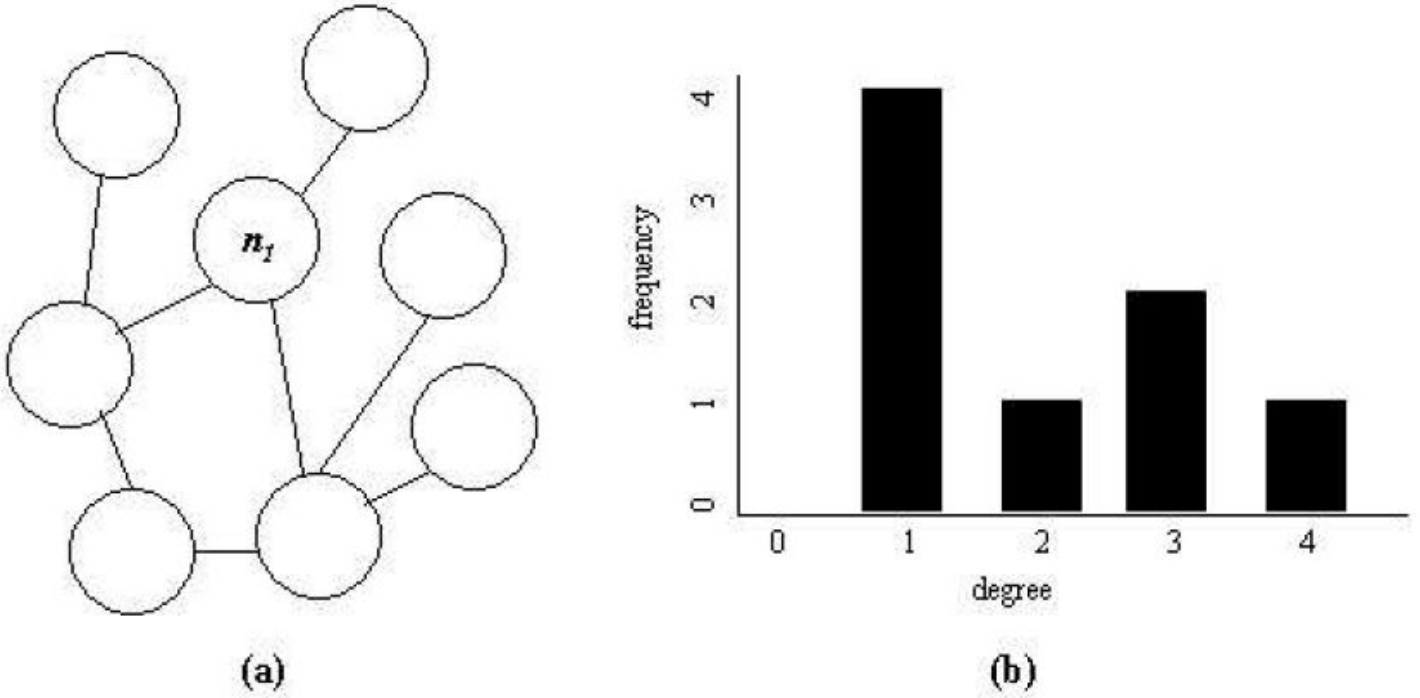


Fig. 1. (a) Example of a network. The node labeled n_1 has degree 3 (i.e., three links to other nodes). (b) Degree distribution of the network.

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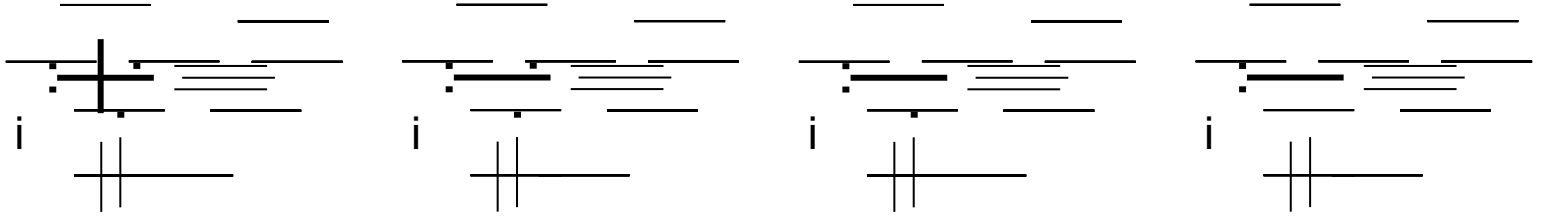
Clusteing Coefficient (C)

The clustering coefficient of a node is the number of connections between its neighbors (*n*) over the maximum number of possible connections between them.

Ci = n / (ki*(ki-1)/2) (being *ki* the degree of the node = number of neighbors)

It gives an idea how clustered or sparse is the neighborhood of a node.



Ci=3/3 =1.0 Ci= 2/3 =0.67 Ci= 1/3 =0.33 Ci= 0/3 =0.0

The clustering coefficient of a graph is the average of the clustering coefficients of all its nodes. It gives an idea of how clustered/interconnected a graph is (vs. “star-like” graphs and trees)

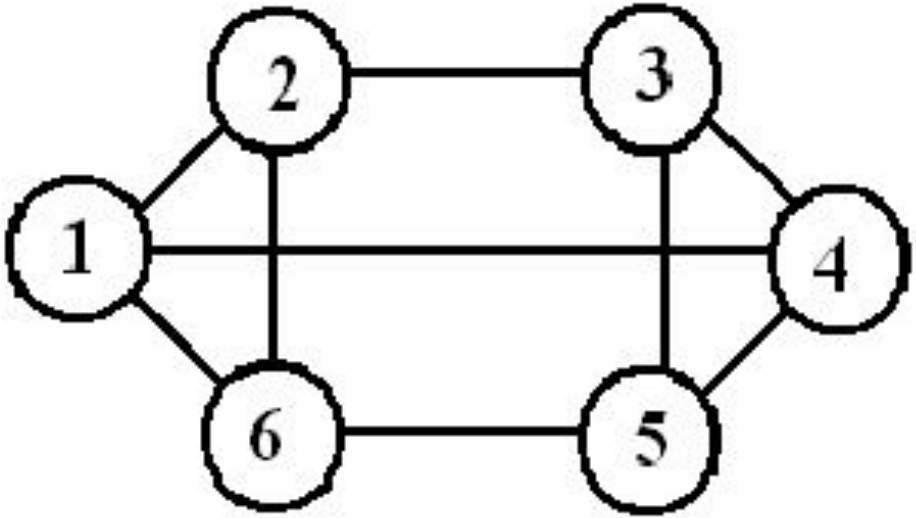
Characteristic path length and diameter

- The characteristic path length is the average of the lengths of the shortest paths (distances) between all nodes
  - $L = \langle d_{ij} \rangle$

- The diameter of a graph is the maximum path length.
  - $D = max(d_{ij})$

Regular graph

- Connected Graph
- All nodes have the same degree (a lattice or grid)



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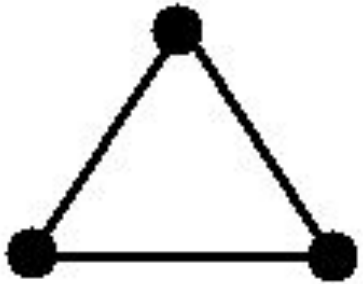
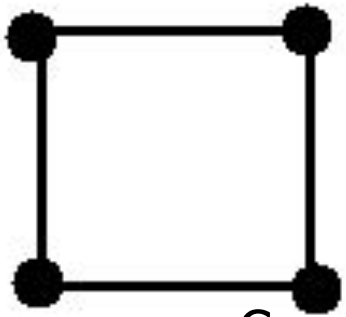
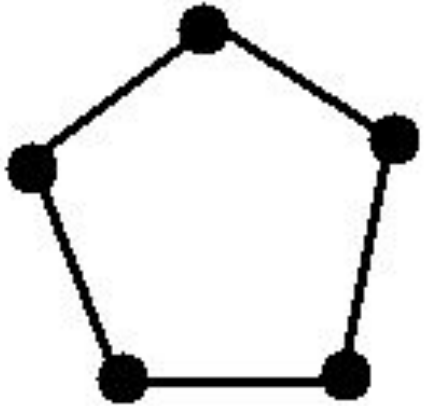
Special regular graph: Cycles



C_3



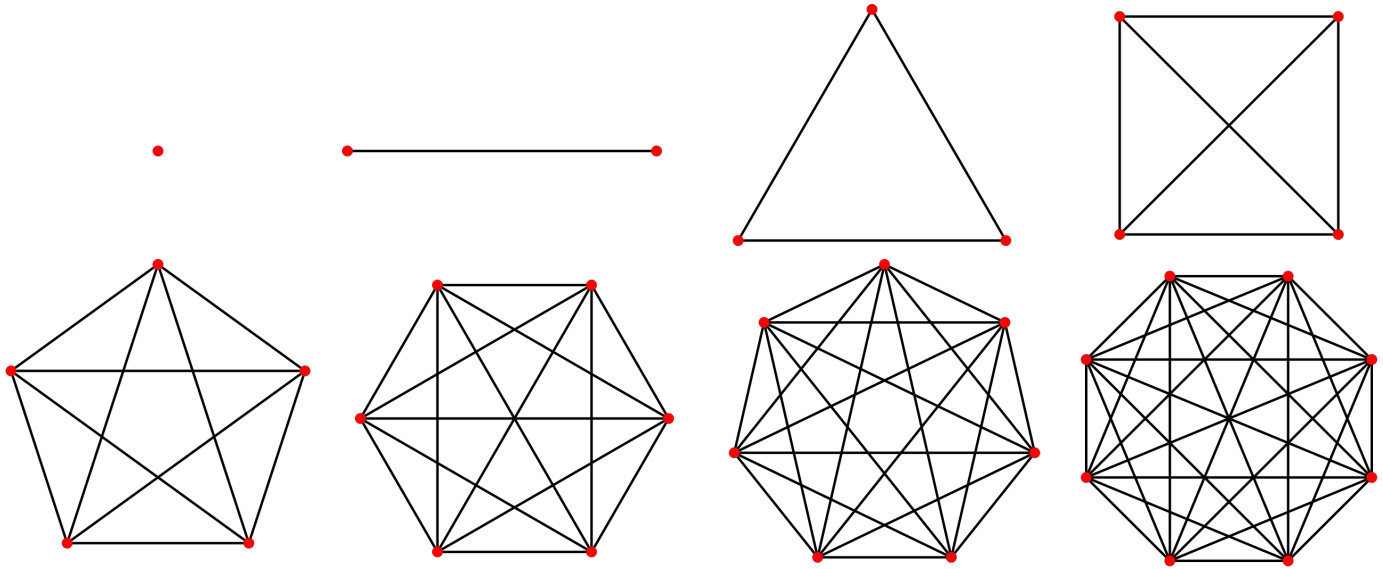
C_4



C_5

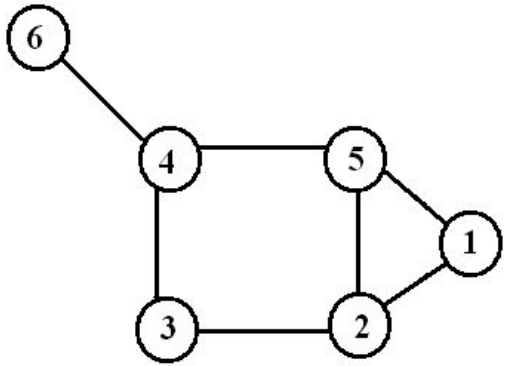
Special regular graph: Complete Graph

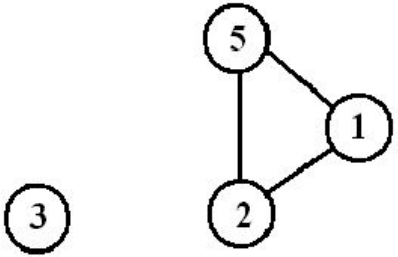
- Every pair of vertices are adjacent
- Has n(n-1)/2 edges



Subgraph

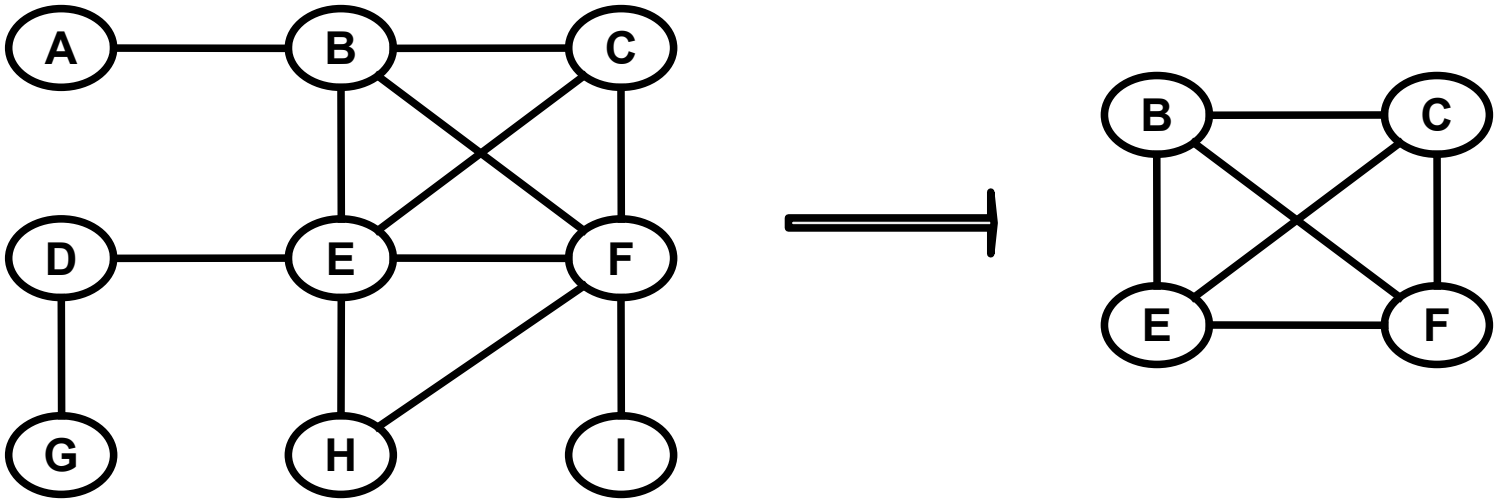
- Vertex and edge sets are subsets of those of G
  - H = (V',E') is a subgraph of G = (V,E) <=> V' $\subseteq$ V, E' $\subseteq$ E
- A **supergraph** of a graph G is a graph that contains G as a subgraph.





Special Subgraph: Cliques

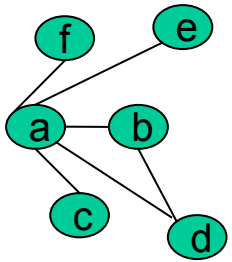
- A clique is a maximum complete connected subgraph.

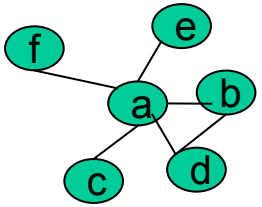


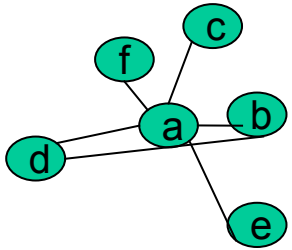
Graph representation: Visual layout

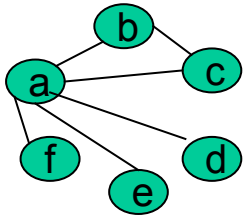
A **layout** is an arrangement of the graph nodes (and edges) in 2D or 3D which facilitates its visualization and/or makes more evident some properties of the graph.

G = ({a, b, c, d, e, f}, (a,b), (a,c), (a,d), (a,e), (a,f), (b,d))

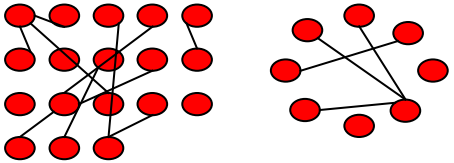




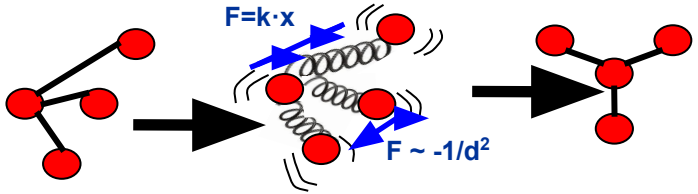




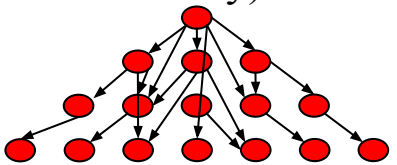
Regular arrangements



Based on "physics"



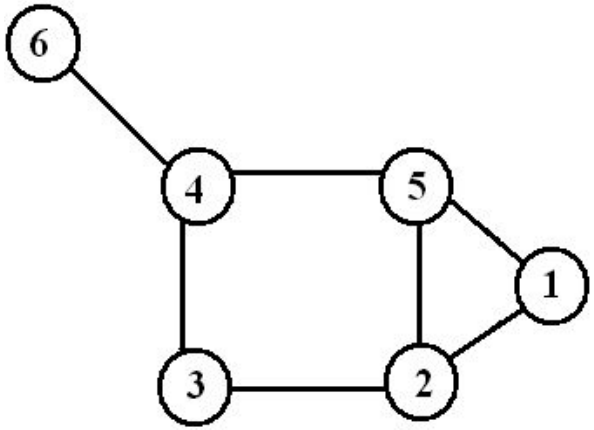
Based on topological properties (e.g. sort by k, to emphasize hierarchy)



Graph representation: Matrix

- **Adjacency Matrix**
  - Dimensions: |V| x |V|
  - Boolean values (adjacent or not)
  - Or Edge Weights
- **Incidence Matrix**
  - Dimensions: |V| x |E|
  - [vertex, edges] contains the edge's data

Graph representation: Matrix



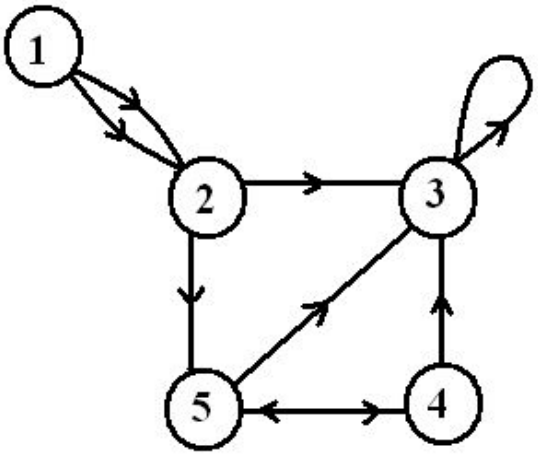
	1	2	3	4	5	6
1	0	1	0	0	1	0
2	1	0	1	0	1	0
3	0	1	0	1	0	0
4	0	0	1	0	1	1
5	1	1	0	1	0	0
6	0	0	0	1	0	0

	1,2	1,5	2,3	2,5	3,4	4,5	4,6
1	1	1	0	0	0	0	0
2	1	0	1	1	0	0	0
3	0	0	1	0	1	0	0
4	0	0	0	0	1	1	1
5	0	1	0	1	0	1	0
6	0	0	0	0	0	0	1

Graph representation: list

- **Edge List**
  - pairs (ordered if directed) of vertices
  - Optionally weight and other data
- **Adjacency List** (node list)
  - an array of |V | lists, one for each vertex in V.
  - For each u ∈ V , ADJ [u] points to all its adjacent vertices.

Graph representation: list



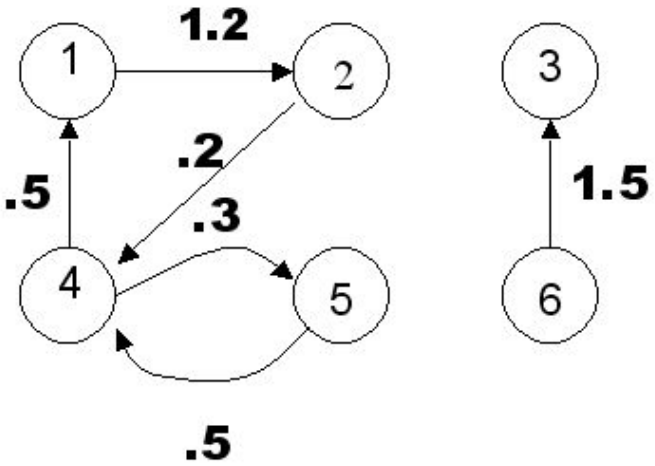
Edge List

- 1 2
- 1 2
- 2 3
- 2 5
- 3 3
- 4 3
- 4 5
- 5 3
- 5 4

Adjacency1 List

- 1 → 2 2
- 2 → 3 5
- 3 → 3
- 4 → 3 5
- 5 → 3 4

Edge Lists for Weighted Graphs

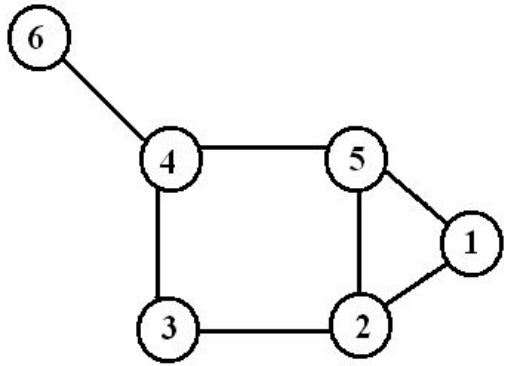


Edge List

. 1 2 1.2
. 2 4 0.2
. 4 5 0.3
. 4 1 0.5
. 5 4 0.5
. 6 3 1.5

Topological Distance

- A **shortest path** between two vertices – a path of minimal length.
- **Length** – number of edges.
- **Distance** between u and v – the length of a shortest path between them (or ∞ if a path does not exist)
- **Distance matrix** D = (d_{ij}) $|V|$ x $|V|$ such that
  d_{ij} is the topological distance between i and j.

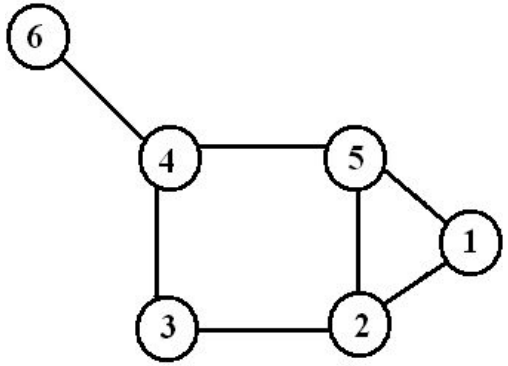


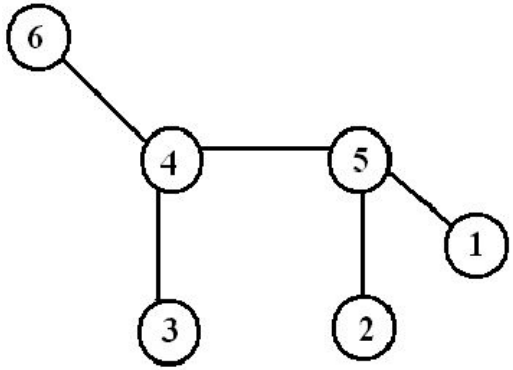
	1	2	3	4	5	6
1	0	1	2	2	1	3
2	1	0	1	2	1	3
3	2	1	0	1	2	2
4	2	2	1	0	1	1
5	1	1	2	1	0	2
6	3	3	2	1	2	0

Graph Algorithm

Spanning tree

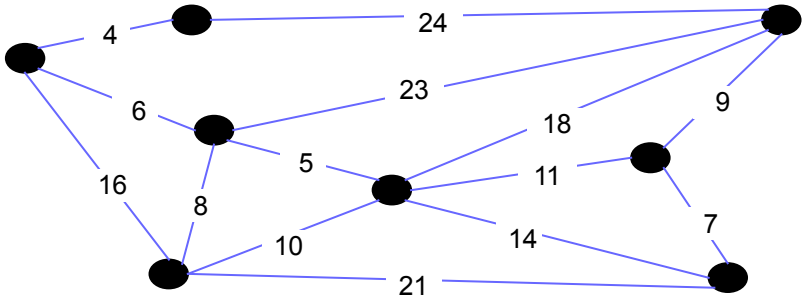
- Let G be a **connected** graph.
- A **spanning tree** in G is a **subgraph** of G that **includes every node** and **is also a tree**.



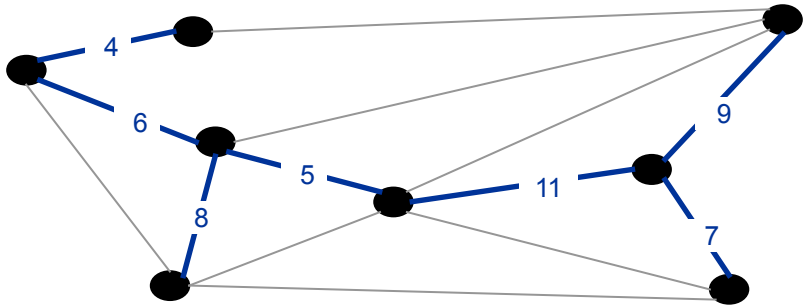


Algorithm: minimum spanning tree

- **Minimum spanning tree**.
- G = (V, E, w) connected weighted graph c_e, an **MST** is a subset of the edges T in E such that T is a spanning tree (contains all nodes of G) whose sum of edge weights is minimized.



G = (V, E)



T, $\Sigma_{e \in T} c_e = 50$

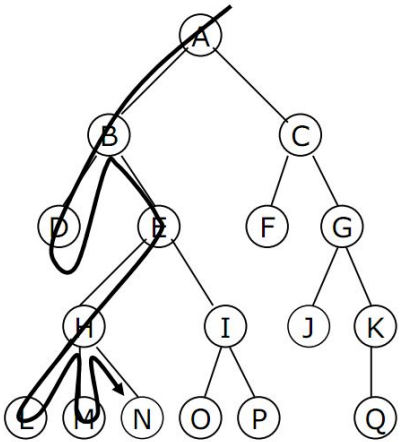
Cayley's Theorem: There are n^{n-2} spanning trees of K_n (can't use brute force).

MST applications

- **Network design:**
  - telephone, electrical, hydraulic, TV cable, computer, road
- **Indirect applications:**
  - identifying functional modules in weighted gene co-expression networks
  - predicting subgraph structure of protein complexess from affinity purification studies
  - Clustering
- Approximation algorithms for **NP-hard** problems:
  - traveling salesperson problem, Steiner tree
  - Kruskal's Algorithm

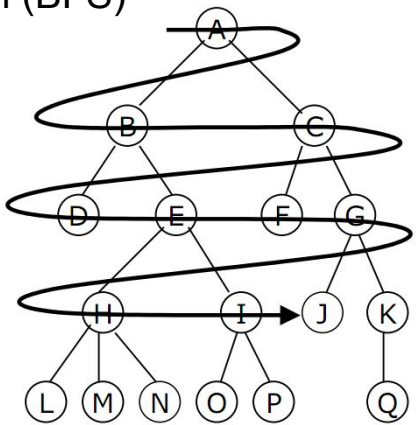
Graph Traversing

- Given a graph G(V,E), explore every vertex and every edge
- Using adjacency list is more efficient
- Example algorithms:
  - Depth-first search (DFS)



DFS

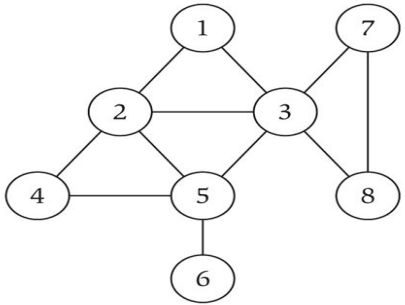
Breadth-first search (BFS)

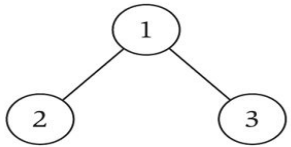


BFS

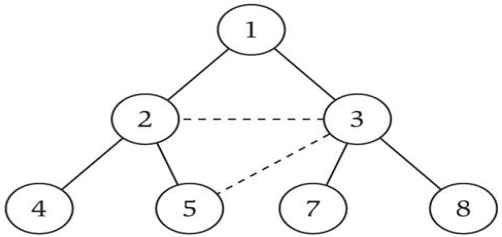
Graph Traversing

- BFS example:

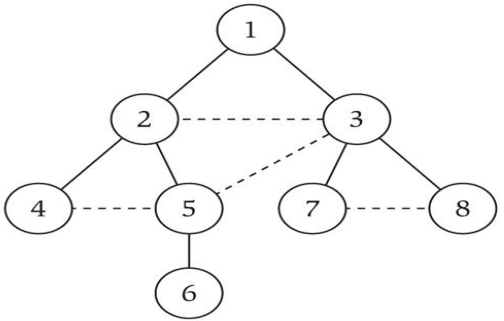




(a)



(b)



(c)

L_0

L_1

L_2

L_3

Graph Traversing

- Running time of BFS: linear, $O(|V|+|E|)$, using adjacency list
- BFS: Python code

```
def dfs(graph, start, visited=None):
    if visited is None:
        visited = set()
    visited.add(start)
    for next in graph[start] - visited:
        dfs(graph, next, visited)
    return visited
```

Graph Traversing

- DFS applications:
  - Determines whether G is connected
  - Computes the connected components of G (strongly connected components of a digraph = directed graph)
  - Path / cycle finding
  - Topological sort (ordering of vertices of digraph G(V,E) such that for every edge (u,v) in E, u appears before v in the ordering)
  - Linear running time

- BFS applications:
  - Computes the distance from s to each reachable vertex in unewighted G
  - Finds shortest paths from s to all other nodes in unweighted G
  - Finds a simple cycle, if there is one
  - Computes the connected components of G

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Bibliography

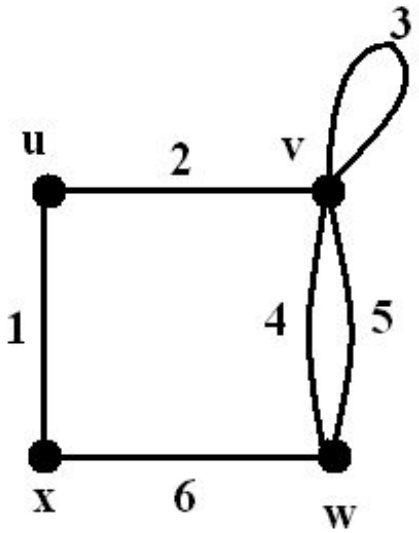
- *"Algorithm design"* - Chapter 3, Jon Kleinberg & Eva Tarods
- *"Graph Theory with Applications"*, J. A. Bondy and U. S. R. Murty
- *"Lecture Notes on Graph Theory"*, Tero Harju
- *"Statistical mechanics of complex networks"* Albert Lazlo Barabasi & Reka Albert
- The web….

Exercise

Exercise 1

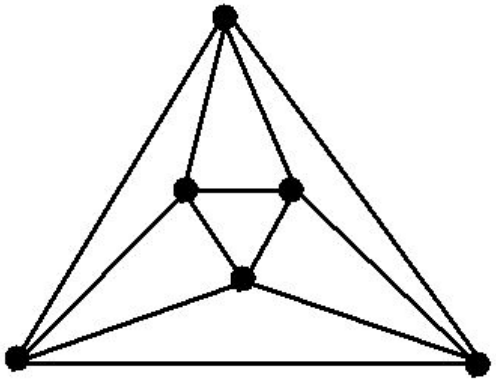
Which of the following statements hold for this graph?

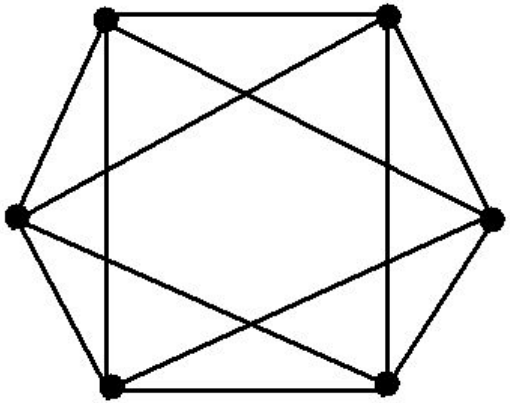
(a) nodes v and w are adjacent;
(b) nodes v and x are adjacent;
(c) node u is incident with edge 2;
(d) edge 5 is incident with node x.



Exercise 2

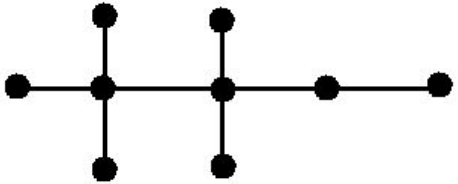
Are the following two graphs isomorphic?



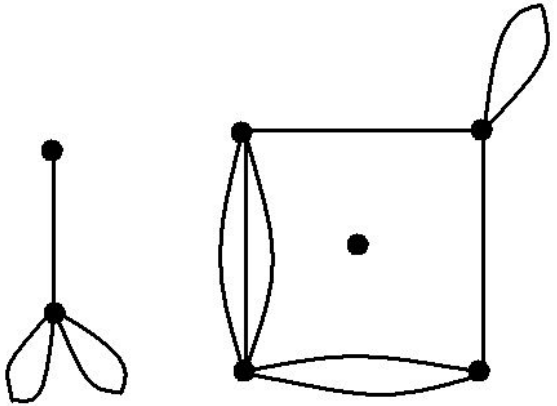


Exercise 3

Write down the degree sequence of each of the following graphs:



(a)



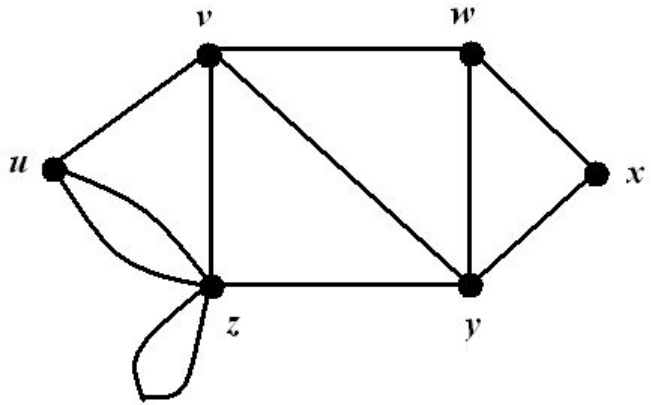
(b)

Exercise 4

Complete the following statements concerning the graph given below:

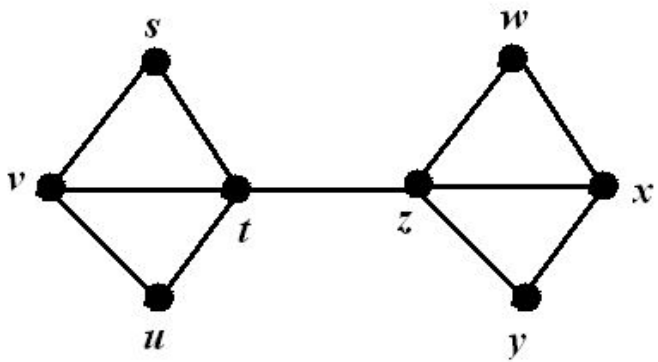
(a) *xyzzvy* is a _____of length____between___and__;

(b) *uvyz* is _____of length ____between___and__.



Exercise 5

Write down all the paths between s and y in the following graph. Build the distance matrix of the graph.



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Exercise 6

Draw the graphs given by the following representations:

Node list

1 2 3 4
2 4
3 4
4 1 2 3
5 6
6 5

Edge list

1 2
1 4
2 2
2 4
2 4
3 2
4 3

Adjacency matrix

	1	2	3	4	5
1	0	2	0	1	1
2	2	0	0	1	1
3	0	0	0	0	0
4	1	1	0	0	2
5	1	1	0	2	0