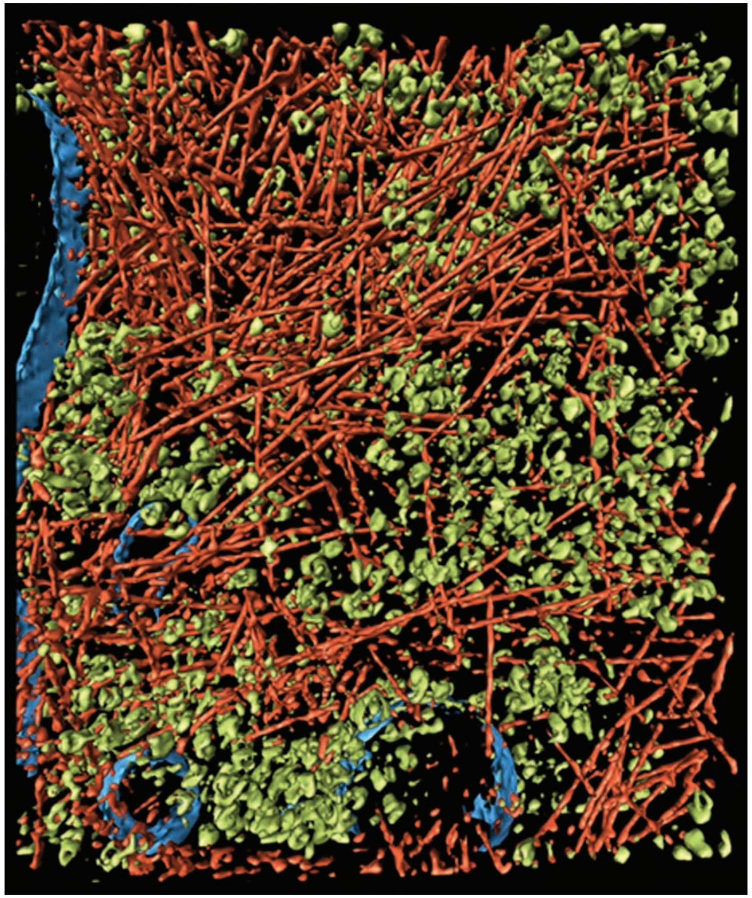
V 1 – Introduction

Tue, Oct 18, 2011

Bioinformatics 3 — Tihamér Geyer

How Does a Cell Work?



Medalia et al, Science 298 (2002) 1209

A cell is a crowded environment
=> many different proteins,
metabolites, compartments, ...

On a microscopic level
=> direct two-body interactions

At the macroscopic level
=> complex behavior

Can we understand the behavior
from the interactions?

=> Connectivity

The Biologist View

Molecular Biology: "One protein — one function"

mutation => phenotype

Linear one-way dependencies: regulation at the DNA level, proteins follow

DNA => RNA => protein => phenotype

Structural Biology: "Protein structure determines the function"

biochemical conditions => phenotype

No feedback, just re-action:

genetic information => molecular structure => biochemical function => phenotype

The Network View of Biology

Molecular Systems Biology: "It's both + molecular interactions"

genetic information => molecular structure => biochemical function => phenotype

molecular interactions

=> highly connected network of various interactions, dependencies

=> study networks

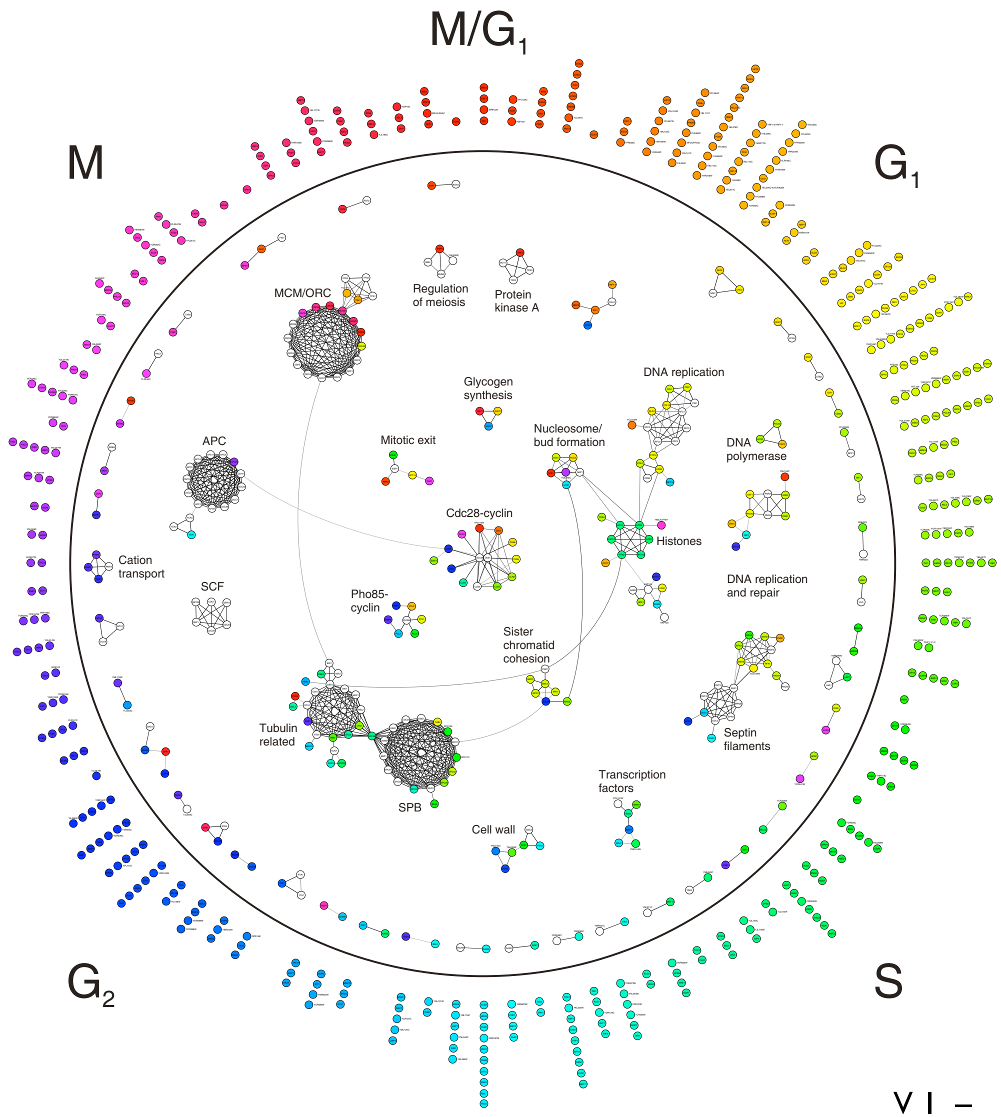
Example: Proteins in the Cell Cycle

From Lichtenberg et al, Science 307 (2005) 724:

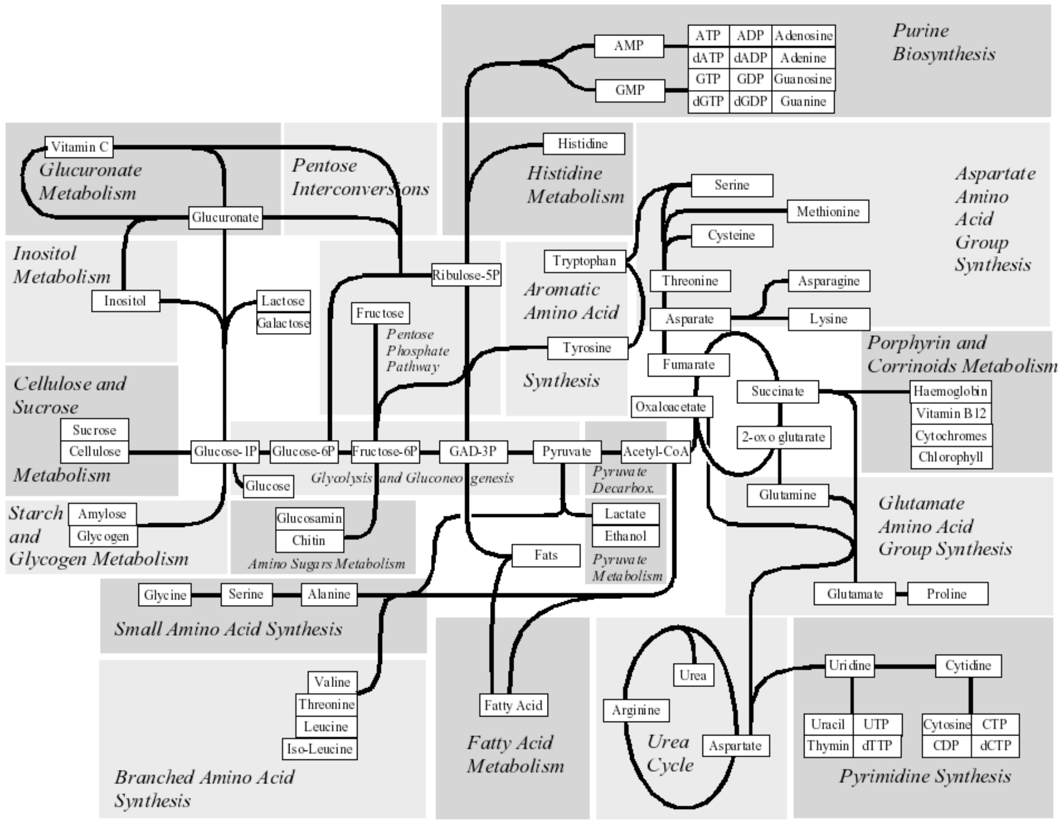
color coded assignment of proteins in time-dependent complexes during the cell cycle

=> protein complexes are transient

=> describe with a time dependent network



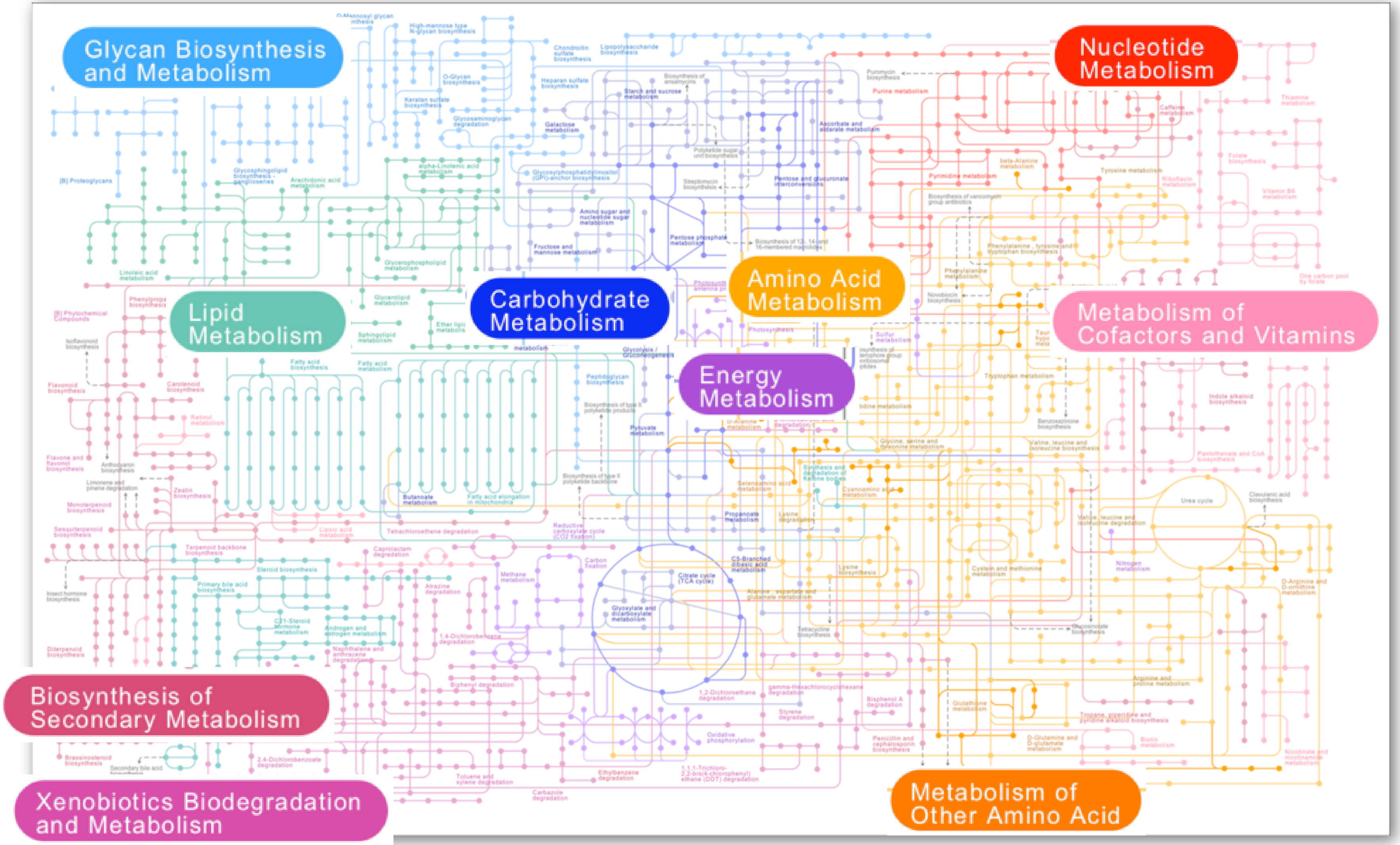
Major Metabolic Pathways



static connectivity <=> dynamic response to external conditions <=> different states during the cell cycle

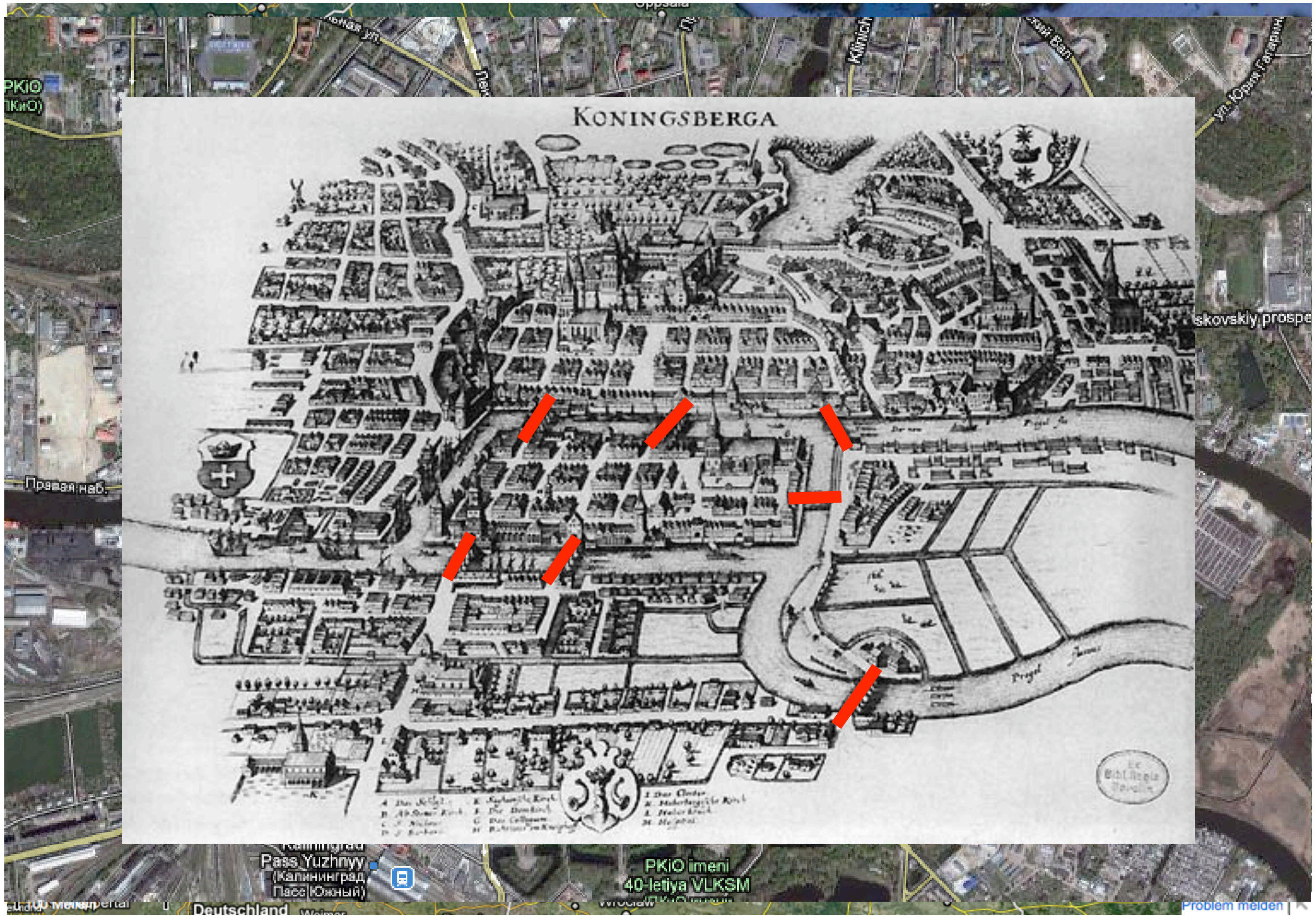
http://www.mvv-muenchen.de/de/netz-bahnhoefe/netzplaene/index.html

Metabolism of *E. coli*



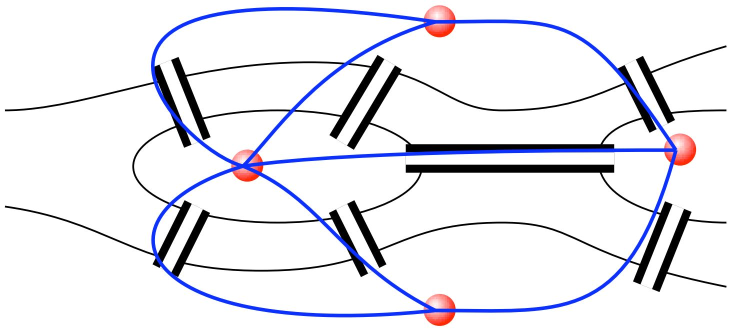
from the KEGG Pathway database

Euler @ Königsberg (1736)



Can one cross all seven bridges once in one continuous (closed) path???

The Königsberg Connections

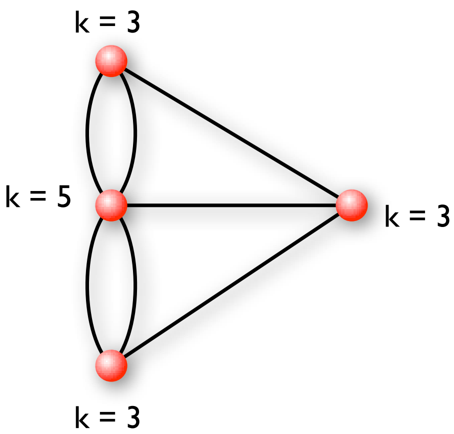


Make it a graph:

i) each neighborhood is a node

ii) each bridge is a link

iii) straighten the layout

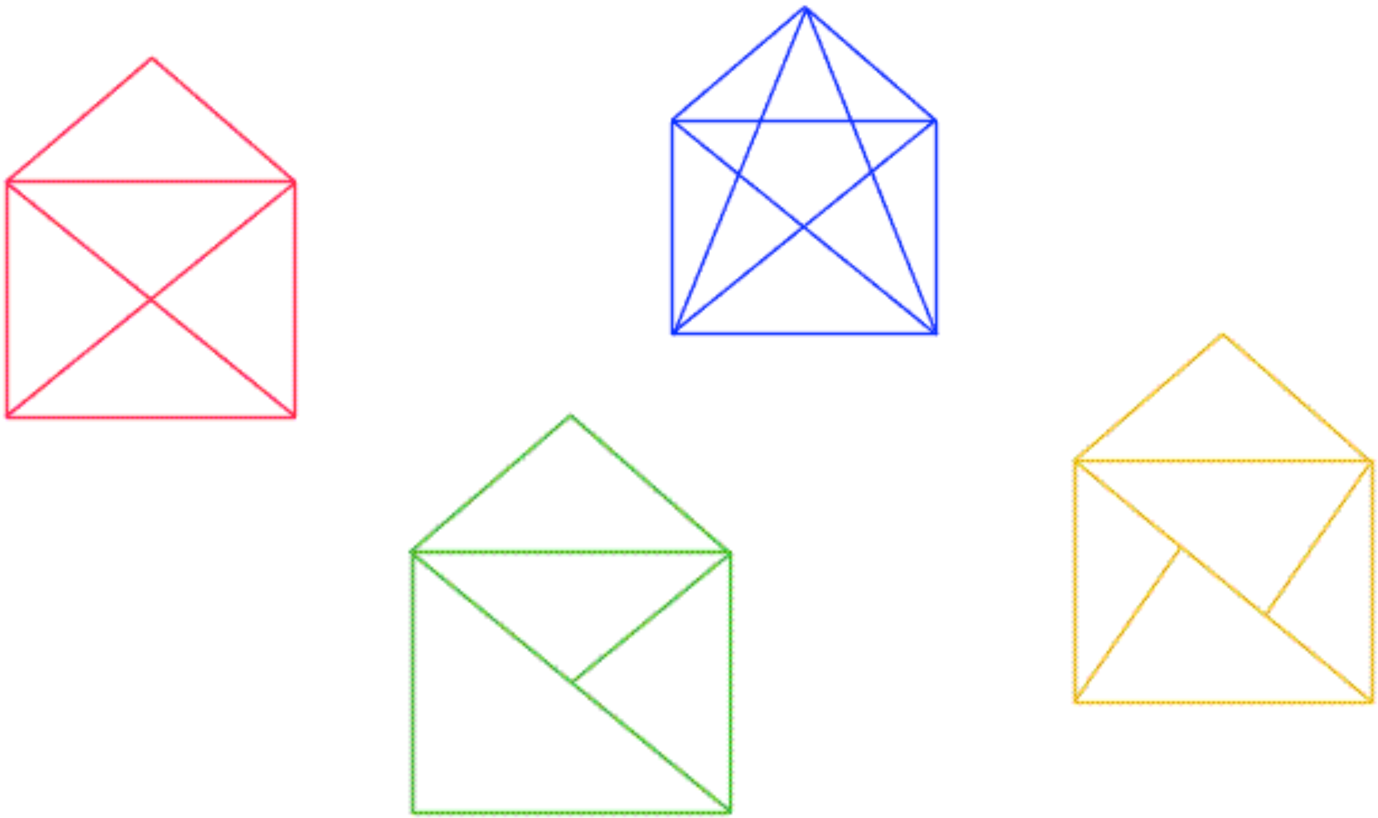


Continuous path
<=> ≤2 nodes with odd degree

Closed continuous path
<=> only nodes with even degree

see also: http://homepage.univie.ac.at/franz.embacher/Lehre/aussermathAnw/Spaziergaenge.html

Draw in one stroke:



http://homepage.univie.ac.at/franz.embacher/Lehre/aussermathAnw/Spaziergaenge.html

Quantify the "Hairy Monsters"

Schwikowski, Uetz, Fields, *Nature Biotech.* **18**, 1257 (2001)

Network Measures:

- No. of edges, links
  => size of the network
- Average degree <k>
  => density of connections
- Degree distribution P(k)
  => structure of the network
- Cluster coefficient C(k)
  => local connectivity
- Connected components
  => subgraphs

Lecture – Overview

Protein-Protein-Interaction Networks: **pairwise** connectivity

=> data from experiments, quality check

PPI: static network **structure**

=> network measures, clusters, modules, …

Gene regulation: cause and **response**

=> Boolean networks

Metabolic networks: steady state of **large networks**

=> FBA, extreme pathways

Metabolic networks: **dynamics**

=> ODEs, modules, stochastic effects

Protein complexes: **spatial** structure

=> experiments, spatial fitting, docking

Protein association:

=> interface properties, spatial simulations

Systems Biology

Literature

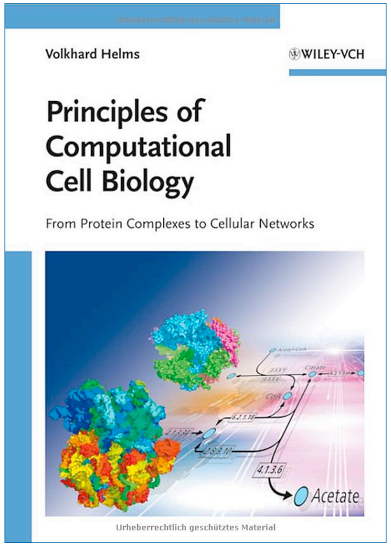
Lecture **slides** — after the lecture

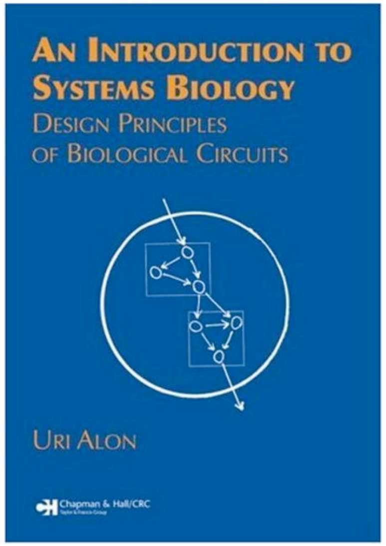
Suggested **reading**

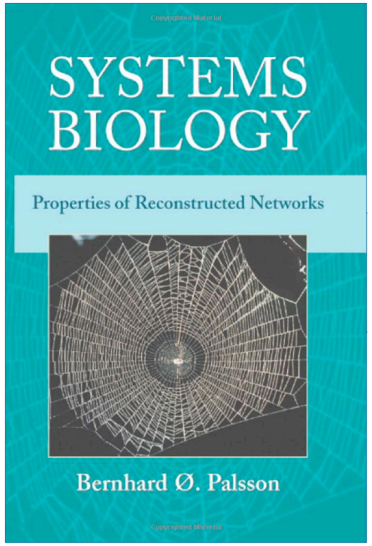
=> check web page

http://gepard.bioinformatik.uni-saarland.de/teaching/…

Textbooks







=> check computer science library

How to Pass

Schein = 3 of 4 short tests + final exam

Short tests: 4 tests of 30-45 min, each
planned: Nov. 8 + Nov. 29? + Dec. 20?? + Jan. 31??
=> average grade from 3 best tests

Final exam: written test of 120 min
requirements:
- 50% of the points from the assignments
- one assignment task presented @ blackboard
- 3 short tests passed

planned: Tue, Feb. 7, 2011???

Assignments

Tutors: Christian Spaniol, Nadine Schaadt

Tutorial: Wed, 12:00–14:00, E2 1, room 007

10 assignments with 100 points each

Assignments are part of the course material (not everything's in the lecture)

=> **one** solution for **two** students

=> hand-written or one **printable** PDF/PS file per email

=> content: data analysis + interpretation — **think!**

=> no 100% solutions required!!!

=> attach the source code of the programs for checking (no supplementary data)

=> present one task at the **blackboard**

Hand in at the following Fri electronically until 13:00 or
printed at the begin of the lecture.

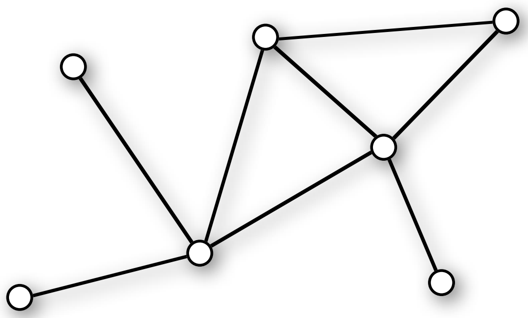
Some Graph Basics

Network <=> Graph

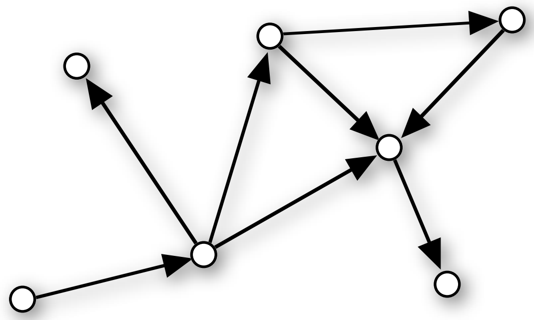
Formal **definition**:

A **graph** G is an ordered pair (V, E) of a set V of **vertices** and a set E of **edges**.

$$G = (V, E)$$



undirected graph



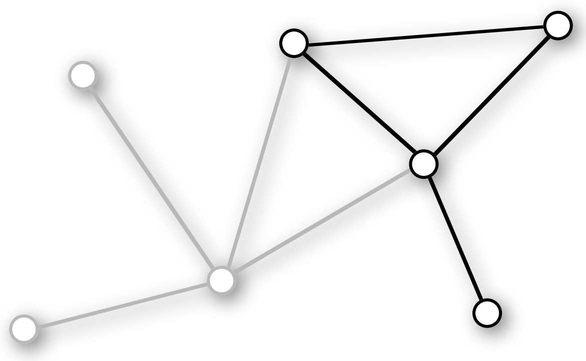
directed graph

If $E = V^{(2)}$ => fully connected graph

Graph Basics II

Subgraph:

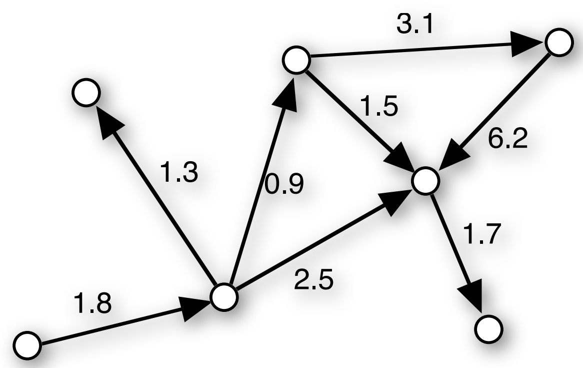
G' = (V', E') is a subset of G = (V, E)



Practical question: how to define useful subgraphs?

Weighted graph:

Weights assigned to the edges



Note: no weights for vertices
=> why???

Walk the Graph

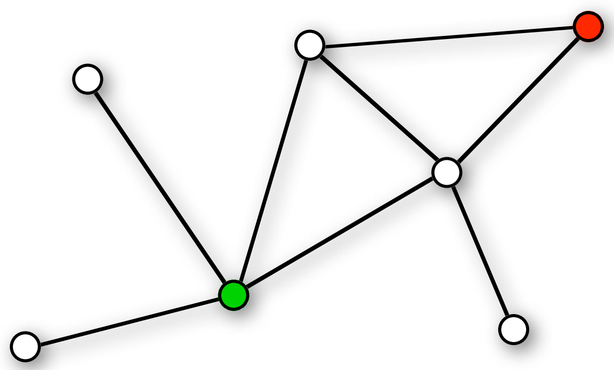
Path = sequence of connected vertices
start vertex => internal vertices => end vertex

Two paths are **independent** (internally vertex-disjoint),
if they have no internal vertices in common.

Vertices u and v are **connected**, if there exists a path from u to v.
otherwise: disconnected

Trail = path, in which all edges are distinct

Length of a path = number of vertices || sum of the edge weights



How many paths connect the green to the red vertex?

How long are the shortest paths?

Find the four trails from the green to the red vertex.

How many of them are independent?

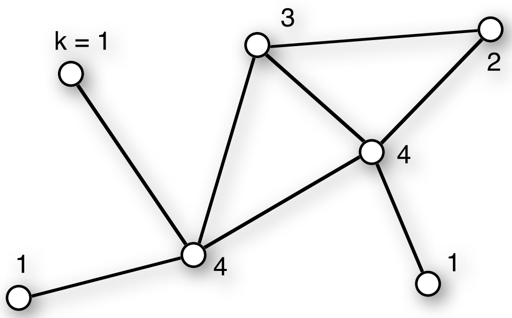
Local Connectivity: Degree

Degree k of a vertex = number of edges at this vertex

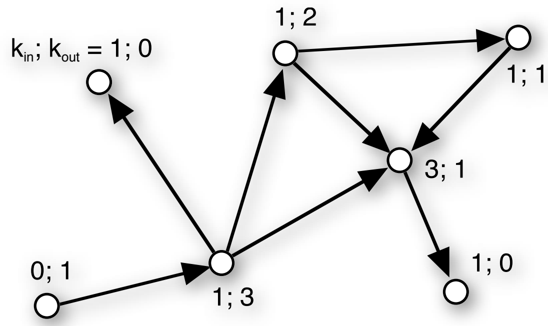
Directed graph => discern k_{in} and k_{out}

Degree distribution P(k) = fraction of nodes with k connections

$$P(k) = \frac{n_k}{N}$$



k	0	1	2	3	4
P(k)	0	3/7	1/7	1/7	2/7



k	0	1	2	3
$P(k_{in})$	1/7	5/7	0	1/7
$P(k_{out})$	2/7	3/7	1/7	1/7

Basic Types: Random Network

Generally: N vertices connected by L edges

More specific: **distribute** the edges **randomly** between the vertices

Maximal number of links between N vertices:

$$L_{max} = \frac{N(N-1)}{2}$$

=> **propability** p for an edge between two randomly chosen nodes:

$$p = \frac{L}{L_{max}} = \frac{2L}{N(N-1)}$$

=> **average degree** λ

$$\lambda = \frac{2L}{N} = p\,(N-1)$$

=> **path lengths** grow with log(N) => small world

Random Network: P(k)

Network with N vertices, L edges
=> Probability for a random link:

$$p = \frac{2L}{N(N-1)}$$

Probability for links to k other nodes at a random node:

$$W_k = p^k \, (1-p)^{N-k-1}$$

Probability that a randomly choosen edge has k links:

$$P(k) = \binom{N-1}{k} W_k = \frac{(N-1)!}{(N-k-1)!\,k!} W_k$$

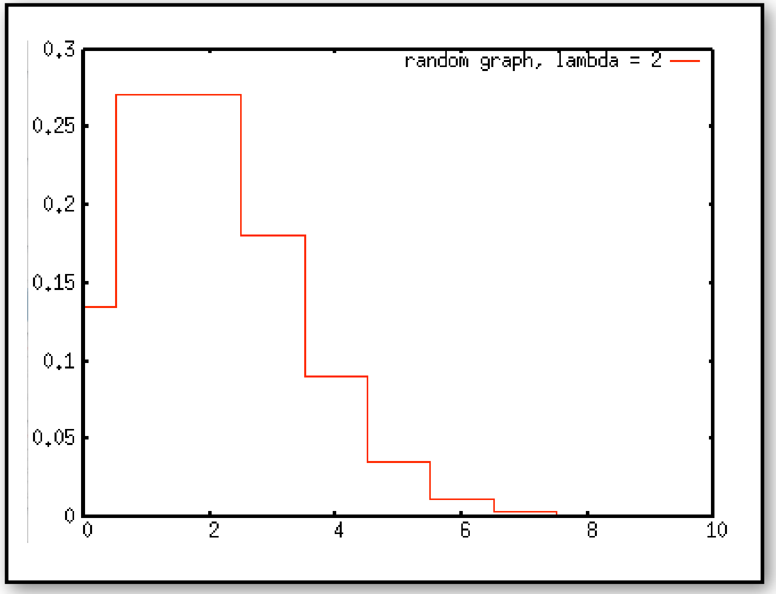
Limit of large graph: N => ∞

$$\begin{aligned}
\lim_{N\to\infty} P(k) &= \lim_{N\to\infty} \frac{N!}{(N-k)!\,k!}\, p^k \,(1-p)^{N-k} \\
&= \lim_{N\to\infty} \left(\frac{N(N-1)\ldots(N-k+1)}{N^k}\right) \frac{\lambda^k}{k!} \left(1-\frac{\lambda}{N}\right)^N \left(1-\frac{\lambda}{N}\right)^{-k} \\
&= \quad 1 \quad \frac{\lambda^k}{k!} \quad \mathrm{e}^{-\lambda} \quad 1 \\
&= \frac{\lambda^k}{k!}\,\mathrm{e}^{-\lambda}
\end{aligned}$$

Random Network: P(k)

Many independently placed edges => Poisson statistics

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



k	P(k | λ = 2)
0	0.135335283237
1	0.270670566473
2	0.270670566473
3	0.180447044315
4	0.0902235221577
5	0.0360894088631
6	0.0120298029544
7	0.00343708655839
8	0.000859271639598
9	0.000190949253244
10	3.81898506488e-05

=> Small probability for $k \gg \lambda$

Basic Types: Scale-Free

Growing network a la Barabasi and Albert (1999):
- start from a small "nucleus"
- add new node with n links
- connect new links to existing nodes with probability α k
  (preferential attachment; β(BA) = 1)

$$p_i = \left(\frac{k_i}{\sum k_i} \right)^\beta$$

=> "the rich become richer"

Properties:

- power-law degree distribution:

$$P(k) \propto k^{-\gamma}$$

with γ = 3 for the BA model

- self-similar structure with highly connected hubs (no intrinsic length scale)
  => path lengths grow with log(log(N))
  => very small world

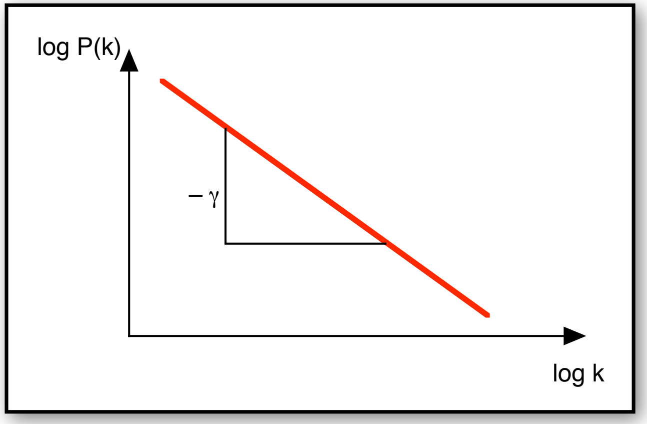
The Power-Law Signature

Plot of a power law $P(k) \propto k^{-\gamma}$

Take log of both sides:

$$\log(P(k)) = -\gamma \log(k)$$

Plot log(P) vs. log(k) => straight line



Note: for fitting γ against experimental data it is often better to use the integrated P(k)
=> integral smoothes the data

$$\int_{k_0}^{k} P(k)dk = \left[-\frac{k^{-(\gamma-1)}}{\Box} \right]_{k_0}^{k}$$

Scale-Free: Examples

The World-Wide-Web:

=> growth via links to portal sites

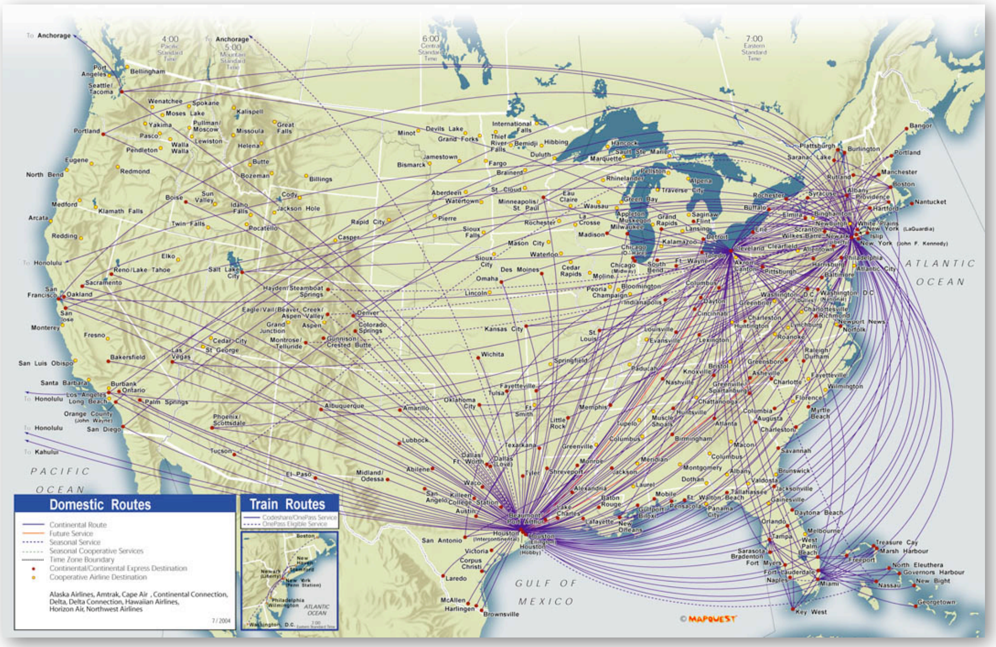
Flight connections between airports

=> large international hubs, small local airports

Protein interaction networks

=> some central,

ubiquitous proteins



http://a.parsons.edu/~limam240/blogimages/16_full.jpg

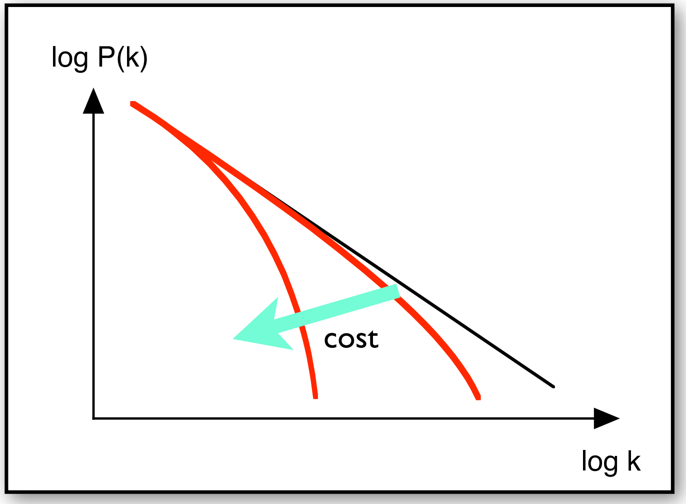
Saturation: Ageing + Costs

Example: network of movie actors

Each actor gets new acquaintances for ~40 years before retirement
=> limits maximum number of links

Example: building up a physical computer network

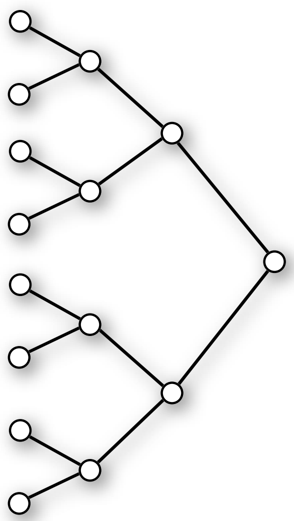
It becomes more an more expensive for a network hub to grow further
=> number of links saturates

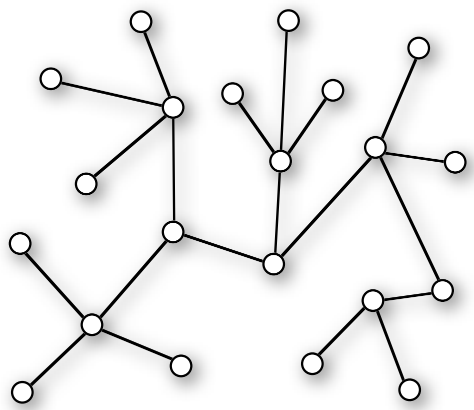


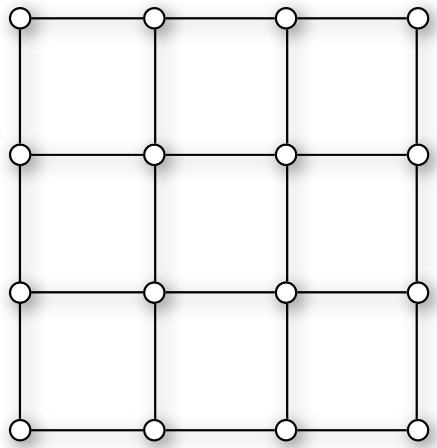
Hierarchical, Regular, Clustered…

Tree-like network with similar degrees
=> like an organigram
=> hierarchic network

All nodes have the same degree
and the same local neighborhood
=> regular network







P(k) for these example networks? (finite size!)

Note: most real-world networks are somewhere inbetween the basic types

Summary

What you learned **today**:

=> **networks** are everywhere

=> how to get the "**Schein**" for BI3

=> basic network **types** and **definitions**:
random, scale-free, degree distribution, Poisson distribution, ageing, …

Next lecture:

=> clusters, percolation

=> algorithm on a graph: Dijkstra's shortest path algorithm

=> looking at graphs: graph layout

Further Reading:
R. Albert and A–L Barabási, „Statistical mechanics of complex networks“
Rev. Mod. Phys. **74** (2002) 47-97