Bioinformatics 3

V 2 – Clusters, Dijkstra, and Graph Layout

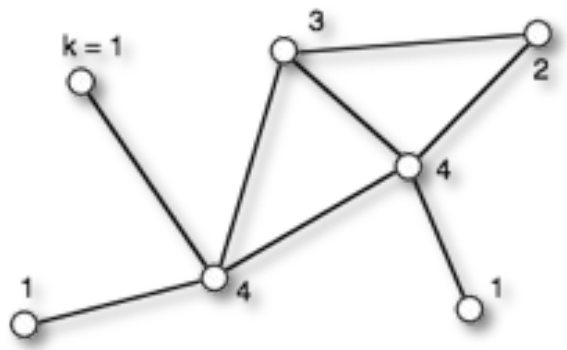
Mon, Oct 21, 2013

Graph Basics

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

Degree distribution *P(k)*

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



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

Random network:

also called the "Erdös-Renyi model"

start from all nodes, add links randomly

P(k) = "Poisson"

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

Scale-free network:

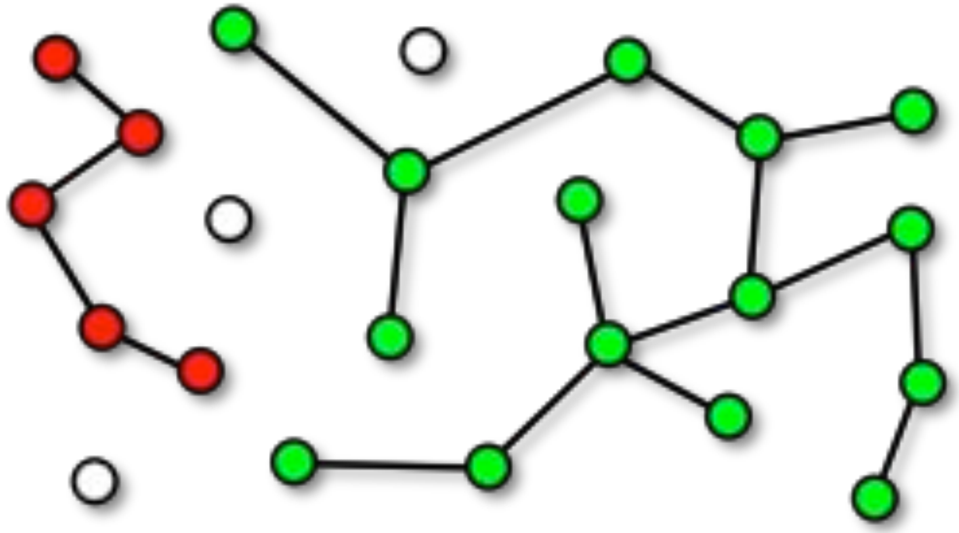
grow with preferential attachment

P(k) = power law

Connected Components

Connected graph <=> there is a path between all pairs of nodes

In large (random) networks: complete $\{V\}$ often not connected
→ identify connected subsets $\{V_i\}$ with $\{V\} = \cup \{V_i\}$
→ **connected components** (CC)



#CC = 5
$N_{max} = 15$
$N_{min} = 1$

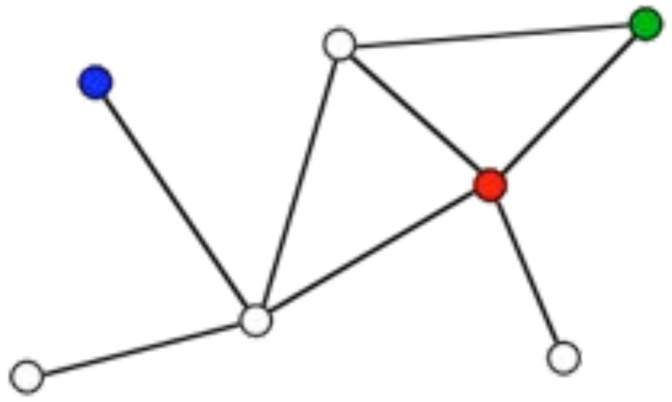
Connectivity of the Neighborhood

How many of the neighboring vertices are themselves neighbors?
=> **clustering coefficient** *C(k)*

Number of possible edges between *k* nodes: $n_{max} = \frac{k(k-1)}{2}$

n_k is the actual number of edges between the neighbor nodes.

Fraction of actual edges ≅ **clustering coefficient** $C(k, n_k) = \frac{2n_k}{k(k-1)}$



green: $k = 2, n_k = 1 \rightarrow C = 1$

red: $k = 4, n_k = 2 \rightarrow C = 1/3$

blue: $k = 1, n_k = ? \rightarrow C$ is not defined

Note: clustering coeff. sometimes also defined via fraction of possible triangles

Clustering Coefficient of a Graph

Data: C_i for each node *i* $\rightarrow$ *N* values

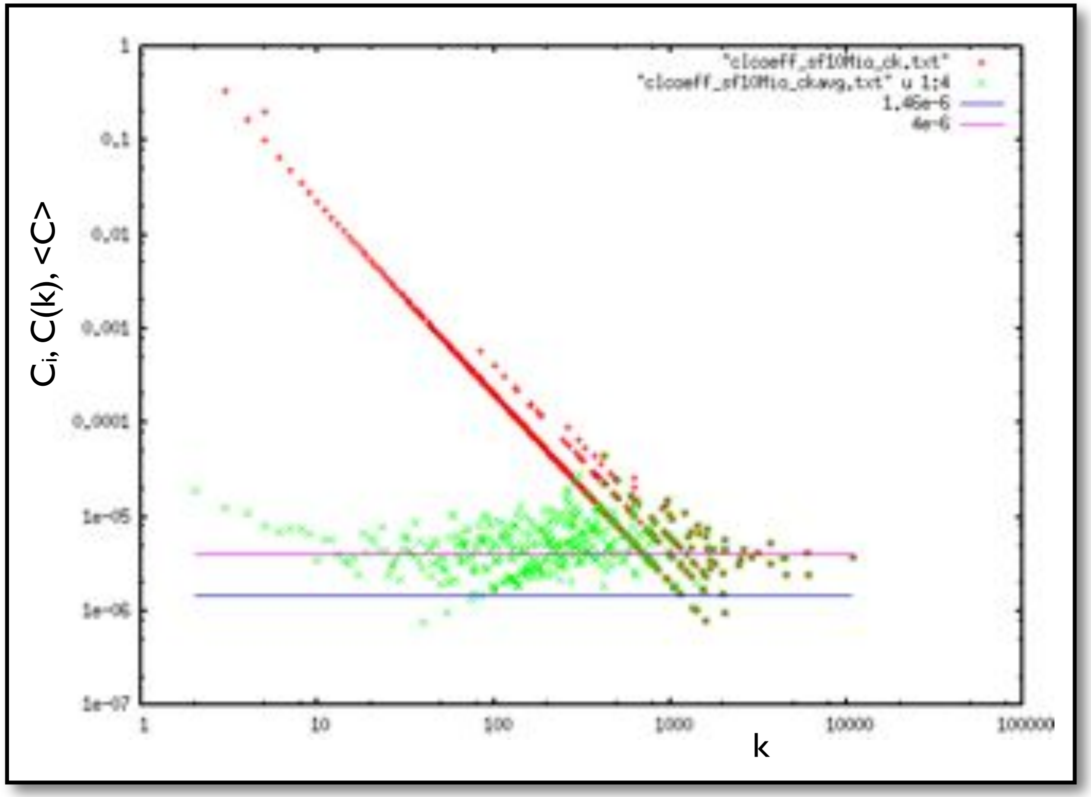
Statistics:

average at **fixed k**

$$\rightarrow \quad C(k) = \frac{1}{n_k} \sum_{k_i = k} C_i$$

average over **all nodes**

$$\rightarrow \quad \langle C \rangle = \frac{1}{N} \sum C_i$$



Note: it is also possible to average the *C(k)*
$\Rightarrow$different value for <*C*> !!!
Because no weighting for different occupancy of k's.

C(k) for a Random Network

Clustering coefficient when *m* edges exist between *k* neighbors

$$C(k,m) = \frac{2m}{k(k-1)}$$

Probability to have exactly *m* edges between the *k* neighbors

$$W(m) = \binom{k}{m} p^m \, (1-p)^{\frac{k(k-1)}{2} - m}$$

Average *C(k)* for degree *k*:

$$C(k) = \frac{\sum_{m=0}^{\frac{k(k-1)}{2}} W(m)\, C(k,m)}{\sum_{m=0}^{\frac{k(k-1)}{2}} W(m)} = \ldots = p$$

→ *C(k)* is independent of *k*

<=> same local connectivity throughout the network

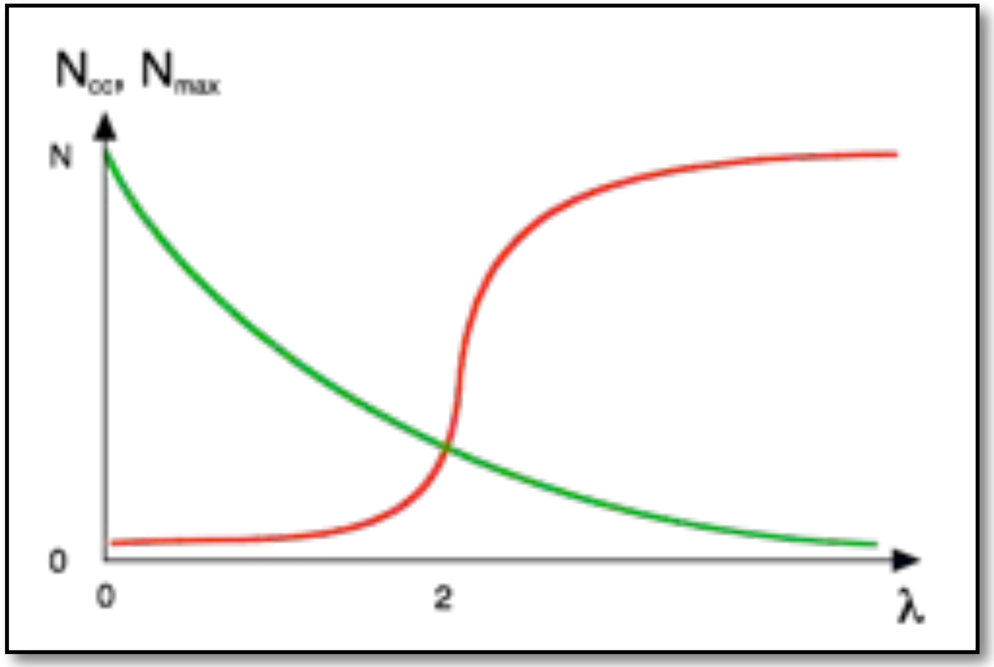
The Percolation Threshold

Connected component = all vertices that are connected by a path

Very few edges
$\Rightarrow$only CCs
of size 2

$\xleftrightarrow{\text{Percolation}}$
transition at
$\lambda = 2$

Lots of edges
$\rightarrow$ graph is one CC



Identify:
N_{cc} = number of connected components (clusters)
N_{max} = size of the largest cluster

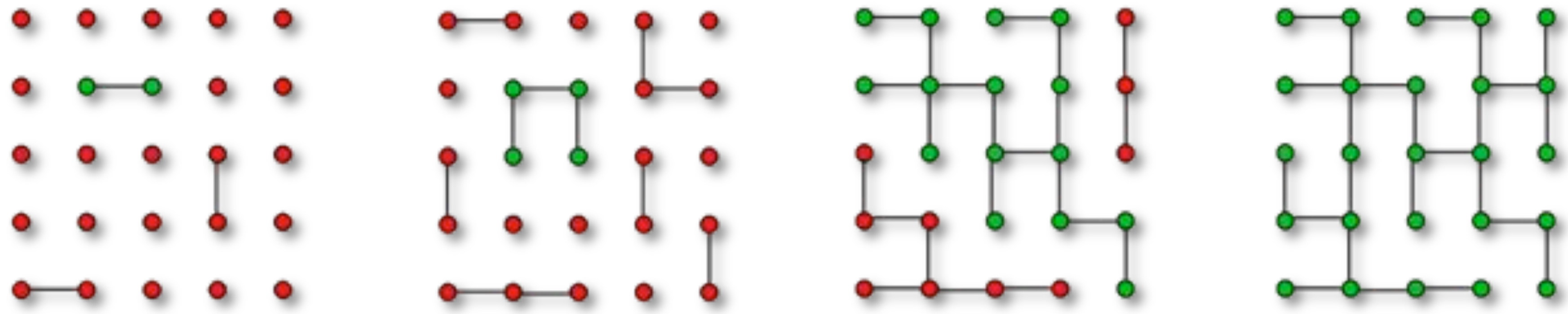
For $\lambda > 2$:
giant
component
exists

average degree λ

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

Percolation Transition

Example: regular square lattice, N = 25 nodes, L_{max} = 40 links between next neighbors



$L = 3$	$L = 11$	$L = 22$	$L = 24$
$\lambda = 0.24$	$\lambda = 0.88$	$\lambda = 1.76$	$\lambda = 1.92$
$N_{cc} = 22$	$N_{cc} = 14$	$N_{cc} = 3$	$N_{cc} = 1$
$N_{max} = 2$	$N_{max} = 4$	$N_{max} = 15$	$N_{max} = 25$

"percolation"

percolation = "spanning structure" emerges (long range connectivity)

for an infinite square lattice: percolation transition at $\lambda = 2$

here: finite size effect <=> fewer possible links at the boundaries

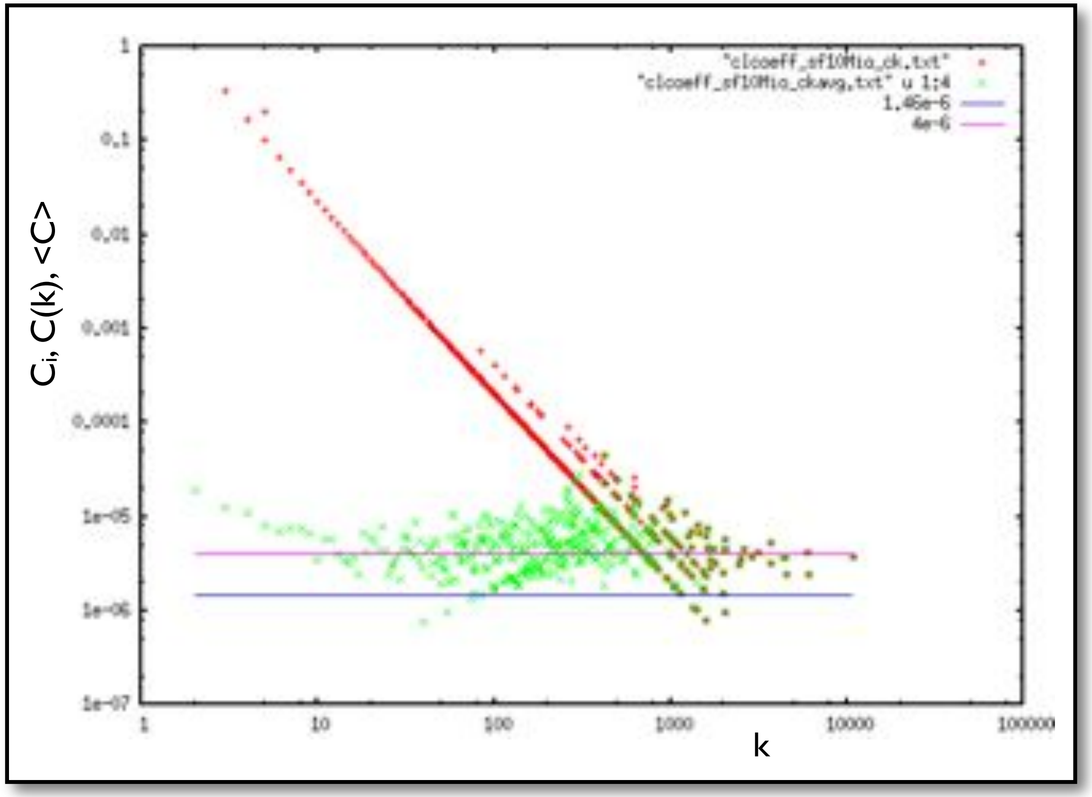
Clusters in scale free graphs

Scale-free network <=> no intrinsic scale

→ same properties at any *k*-level

→ same local connectivity

→ *C(k)* = const.



"Real" biological data

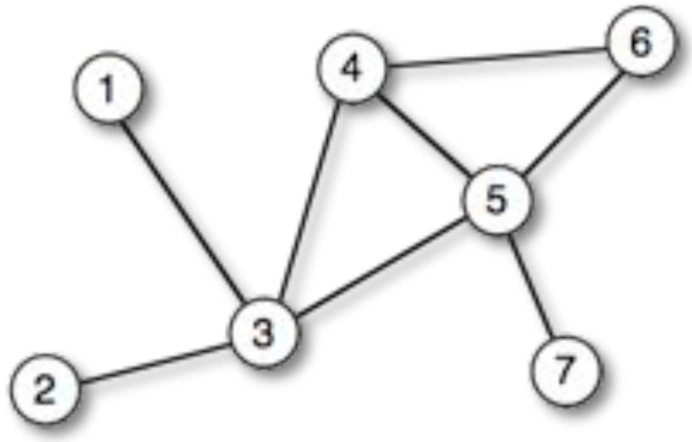
→ missing links

→ multiple clusters

Is the metabolic network of a cell fully connected?

Algorithms on Graphs

How to **represent** a graph in the **computer**?



1. **Adjacency list**

=> list of neighbors for each node

1:	(3)
2:	(3)
3:	(1, 2, 4, 5)
4:	(3, 5, 6)
5:	(3, 4, 6, 7)
6:	(4, 5)
7:	(5)

+ minimal memory requirement

+ vertices can easily be added or removed

– requires $O(\lambda)$ time to determine whether a certain edge exists

Note: for weighted graphs store pairs of (neighbor label, edge weight)

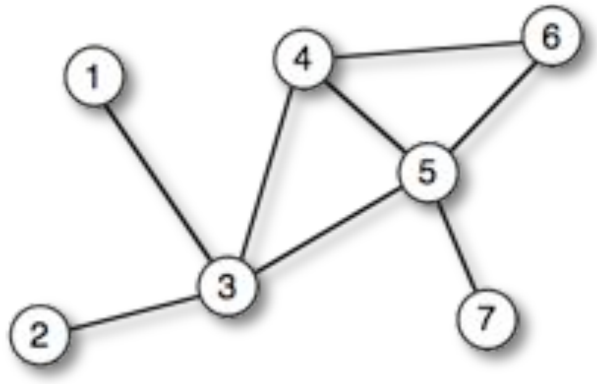
Graph Representation II

2. **Adjacency matrix**

→ *N* x *N* matrix with entries M_{uv}

M_{uv} = weight when edge between *u* and *v* exists,
0 otherwise

→ symmetric for undirected graphs



	1	2	3	4	5	6	7
1	–	0	1	0	0	0	0
2	0	–	1	0	0	0	0
3	1	1	–	1	1	0	0
4	0	0	1	–	1	1	0
5	0	0	1	1	–	1	1
6	0	0	0	1	1	–	0
7	0	0	0	0	1	0	–

+ fast *O(1)* lookup of edges
– large memory requirements
– adding or removing nodes is expensive

Note: very convenient in programming languages that support sparse multi-dimensional arrays
=> Perl

Graph Representation III

3. **Incidence matrix**

→ N x M matrix with entries M_{nm}

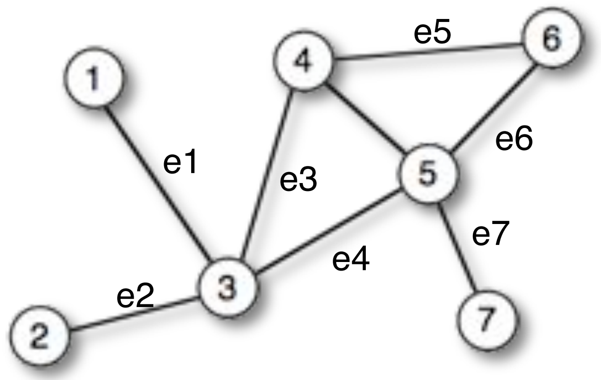
M_{nm} = weight when edge m ends at node n

0 otherwise

→ for a plain graph there are two entries per column

→ directed graph:
indicate direction via sign (in/out)

The incidence matrix is a special form of the stoichiometric matrix of reaction networks.



	e1	e2	e3	e4	e5	e6	e7
1	1						
2		1					
3	1	1	1	1			
4			1		1		
5				1		1	1
6					1	1	
7							1

The Shortest Path Problem

Problem:
Find the shortest path from a given vertex
to the other vertices of the graph (Dijkstra 1959).

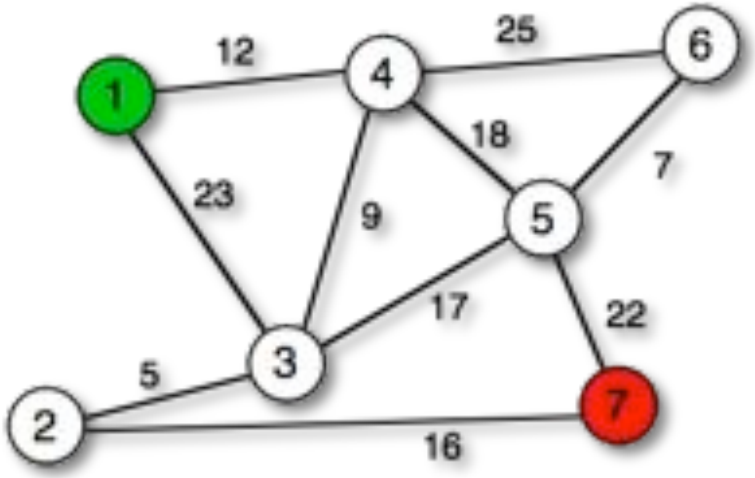
We need (input):
- weighted graph *G(V, E)*
- start (source) vertex *s* in *G*

We get (output):
- shortest distances *d[v]* between *s* and *v*
- shortest paths from *s* to *v*

Edsger Dijkstra (1930-2002):

Idea: Always proceed with the closest node
$\rightarrow$ greedy algorithm

Real world application:
$\rightarrow$ GPS navigation devices



Dijkstra Algorithm 0

Initialization:

```
for all nodes v in G:
    d[v] = oo
    pred[v] = nil
d[s] = 0
```

distance and path to all other nodes is still unknown

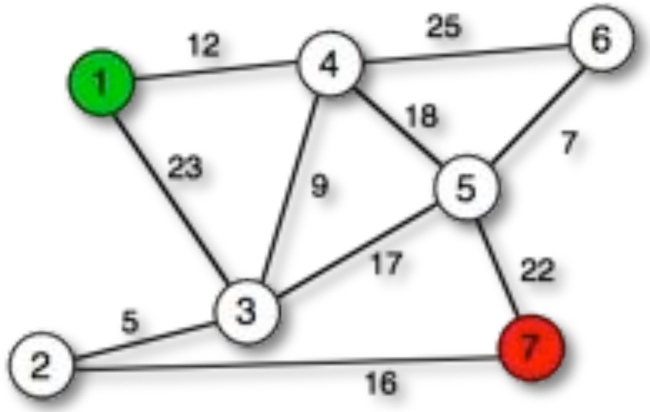
distance from source to source = 0

d[v] = length of path from *s* to *v*

pred[v] = predecessor node on the shortest path

In the example: *s* = 1

node	1	2	3	4	5	6	7
d	0	oo	oo	oo	oo	oo	oo
pred	–	–	–	–	–	–	–



Dijkstra I

Iteration:

```
Q = V
while Q is not empty:
    u = node with minimal d

    if d[u] = oo:
        break

    delete u from Q

    for each neighbor v of u:
        d_temp = d[u] + d(u,v)

        if d_temp < d[v]:
            d[v] = d_temp
            pred[v] = u

return pred[]C
```

Save {*V*} into working copy *Q*

choose node closest to *s*

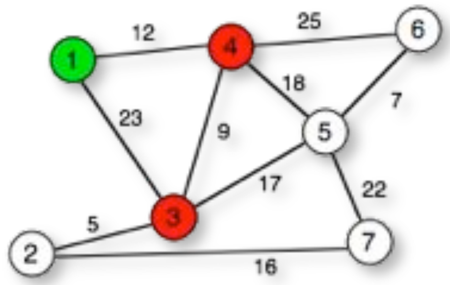
exit if all remaining nodes are inaccessible

calculate distance to *u*'s neighbors

if new path is shorter => update

Dijkstra-Example

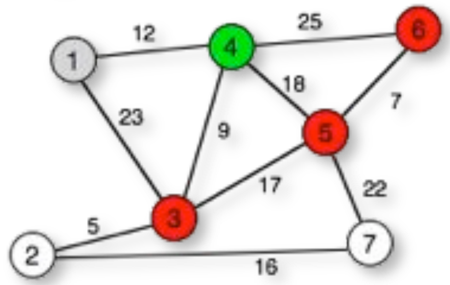
1)



Q = (**1**, 2, 3, 4, 5, 6, 7)

node	**1**	2	3	4	5	6	7
d	**0**	oo	23	12	oo	oo	oo
pred	–	–	1	1	–	–	–

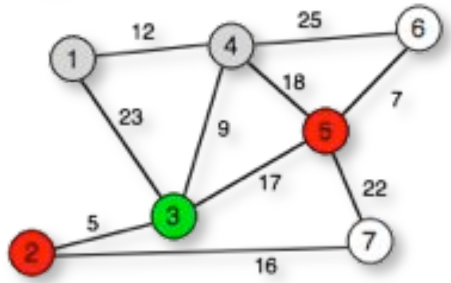
2)



Q = (2, 3, **4**, 5, 6, 7)

node	1	2	3	**4**	5	6	7
d	0	oo	21	**12**	30	37	oo
pred	–	–	4	**1**	4	4	–

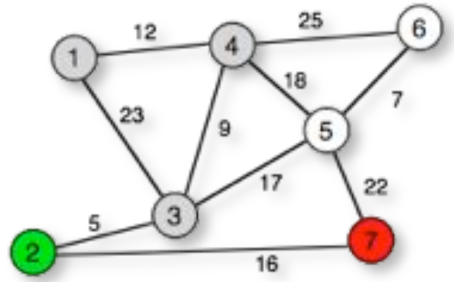
3)



Q = (2, **3**, 5, 6, 7)

node	1	2	**3**	4	5	6	7
d	0	26	**21**	12	30	37	oo
pred	–	3	**4**	1	4	4	–

4)



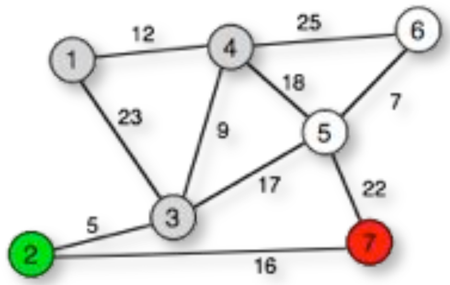
Q = (**2**, 5, 6, 7)

node	1	2	**3**	4	5	6	7
d	0	26	**21**	12	30	37	42
pred	–	3	**4**	1	4	4	2

```
Q = V
while Q is not empty:
   u = node with minimal d

   if d[u] = oo:
      break

   delete u from Q

   for each neighbor v of u:
      d_temp = d[u] + d(u,v)

      if d_temp < d[v]:
         d[v] = d_temp
         pred[v] = u

return pred[]C
```

Example contd.

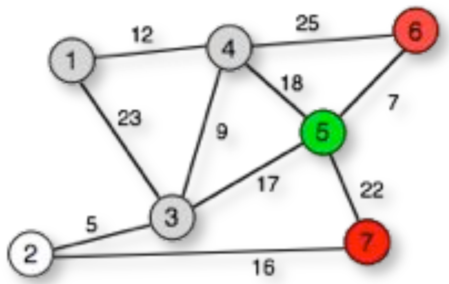
4)



Q = (**2**, 5, 6, 7)

node	1	2	**3**	4	5	6	7
d	0	26	**21**	12	30	37	42
pred	–	3	**4**	1	4	4	2

5)



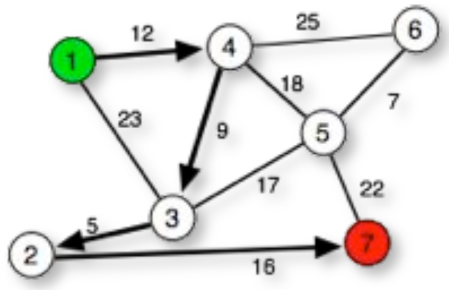
Q = (**5**, 6, 7)

node	1	2	3	4	**5**	6	7
d	0	26	21	12	**30**	37	42
pred	–	3	4	1	**4**	4	2

Q = (**6**, 7)

Final result:

Q = (**7**)



node	1	2	3	4	5	6	7
d	0	26	21	12	30	37	42
pred	–	3	4	1	4	4	2

d(1, 7) = 42 path = (1, 4, 3, 2, 7)

d(1, 6) = 37 path = (1, 4, 6) or (1,4,5,6)

Beyond Dijkstra

Dijkstra works for directed and undirected graphs with **non-negative** weights.

Straight-forward implementation: $O(N^2)$

Graphs with positive and negative weights
→ **Bellman-Ford**-algorithm

If there is a heuristic to estimate weights:
→ improve efficiency of Dijkstra
→ **A***-algorithm

Graph Layout

Task: visualize various interaction data:

e.g. **protein interaction data** (undirected):
- nodes – proteins
- edges – interactions

metabolic pathways (directed)
- nodes – substances
- edges – reactions

regulatory networks (directed):
- nodes – transcription factors + regulated proteins
- edges – regulatory interaction

co-localization (undirected)
- nodes – proteins
- edges – co-localization information

homology (undirected/directed)
- nodes – proteins
- edges – sequence similarity (BLAST score)

Graph Layout Algorithms

Graphs encapsulate relationship between objects
→ drawing gives **visual impression** of these relations

Good Graph Layout: **aesthetic**
- minimal edge crossing
- highlight symmetry (when present in the data)
- even spacing between the nodes

Many approaches in literature (and in software tools),
most useful ones usually NP-complete (exponential runtime)

Most popular for **straight-edge-drawing**:
→ **force-directed**: spring model or spring-electrical model
→ **embedding** algorithms like H3 or LGL

Force-Directed Layout

Peter Eades (1984): graph layout heuristic

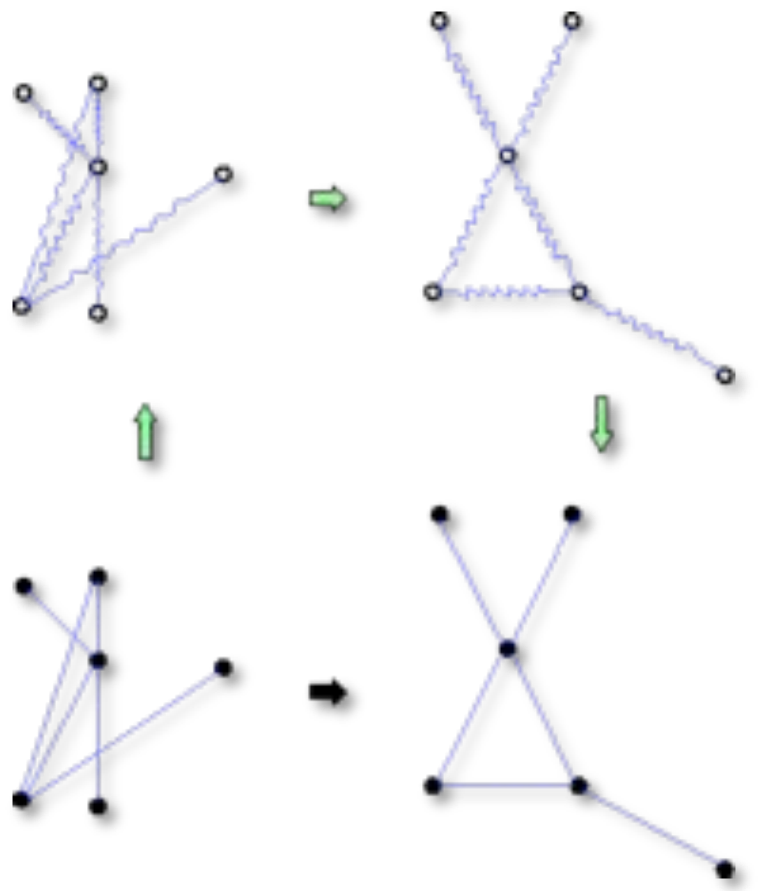
→"**Spring Embedder**" algorithm.

- edges → springs
  vertices → rings that connect the springs

- Layout by dynamic relaxation

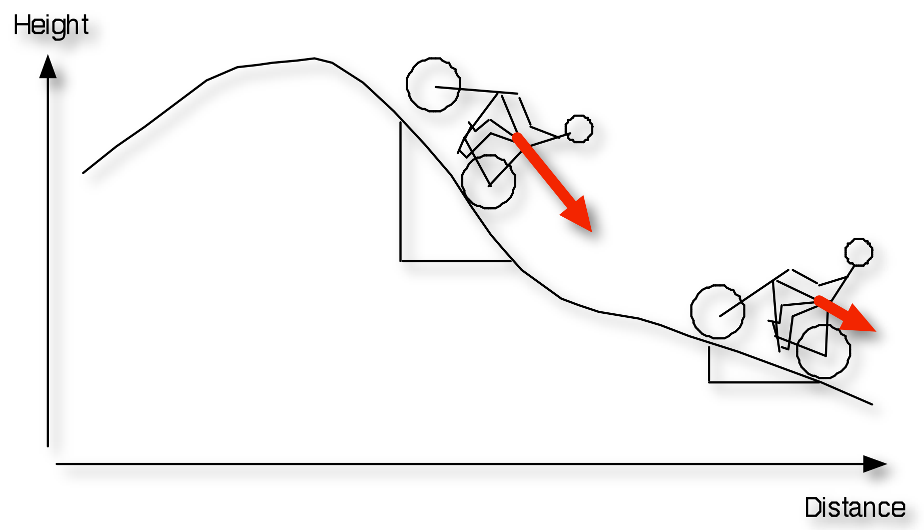
→ lowest-energy conformation

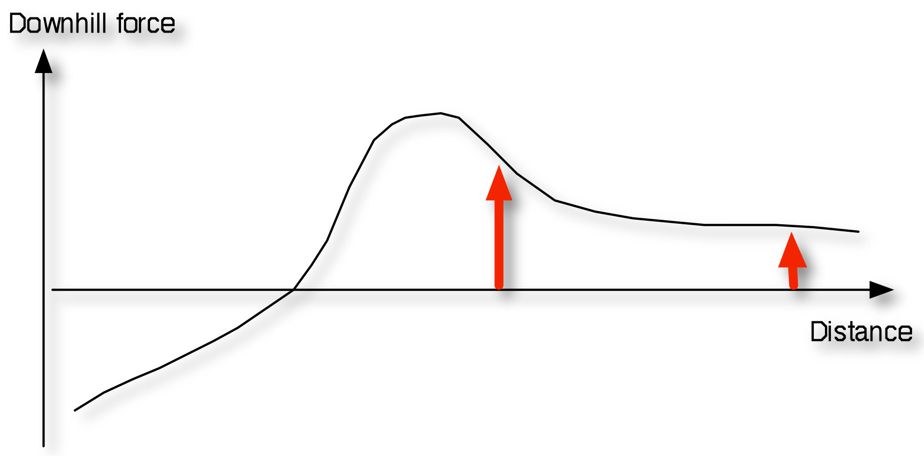
→ "**Force Directed**" algorithm



http://www.hpc.unm.edu/~sunls/research/treelayout/node1.html

Energy and Force





Energy: describes the altitude of the landscape

$$E(x) = mgh(x)$$

Energy increases when you go up the hill

$\updownarrow$

You need more force for a steeper ascent

$$F(x) = -\frac{dE(x)}{dx}$$

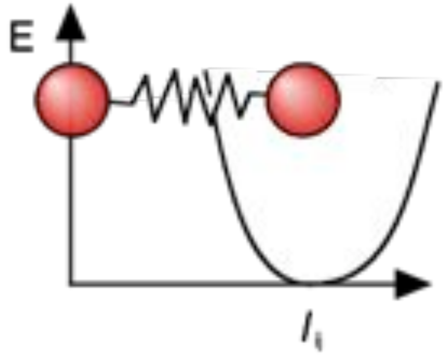
Force: describes the change of the altitude, points downwards.

Spring Embedder Layout

Springs regulate the mutual distance between the nodes

• too close → repulsive force

• too far → attractive force



Spring embedder algorithm:

• add springs for all edges

• add loose springs to all non-adjacent vertex pairs

Total energy of the system:

$$E = \sum_{i=1}^{|V|-1} \sum_{j=i+1}^{|V|} \frac{R}{l_{ij}^2} \left(|x_i - x_j| - l_{ij}\right)^2$$

x_i, x_j = position vectors for nodes *i* and *j*

l_{ij} = rest length of the spring between *i* and *j*

R = spring constant (stiffness)

Problem: l_{ij} have to be determined a priori, e.g., from network distance

Spring Model Layout

Task: find configuration of **minimal energy**

In 2D/3D: force = negative gradient of the energy

$$\vec{F}(\vec{x}) = -\nabla E(\vec{x}) = -\begin{pmatrix} \frac{\partial E}{\partial x} \\ \frac{\partial E}{\partial y} \\ \frac{\partial E}{\partial z} \end{pmatrix}$$

→ Iteratively **move** nodes "**downhill**" along the gradient of the energy

→ displace nodes **proportional** to the **force** acting on them

Problems:

• local minima

• a priori knowledge of all spring lengths

→ works best for regular grids

The Spring-Electrical-Model

More general model than spring embedder model: use two types of forces

1) **attractive harmonic** force between connected nodes (springs)

$$F_{ij}^{h} = -k\,|r_i - r_j|$$

one uses usually the same spring constant *k* for all edges

2) **repulsive Coulomb**-like force between all nodes
"all nodes have like charges" $\rightarrow$ repulsion

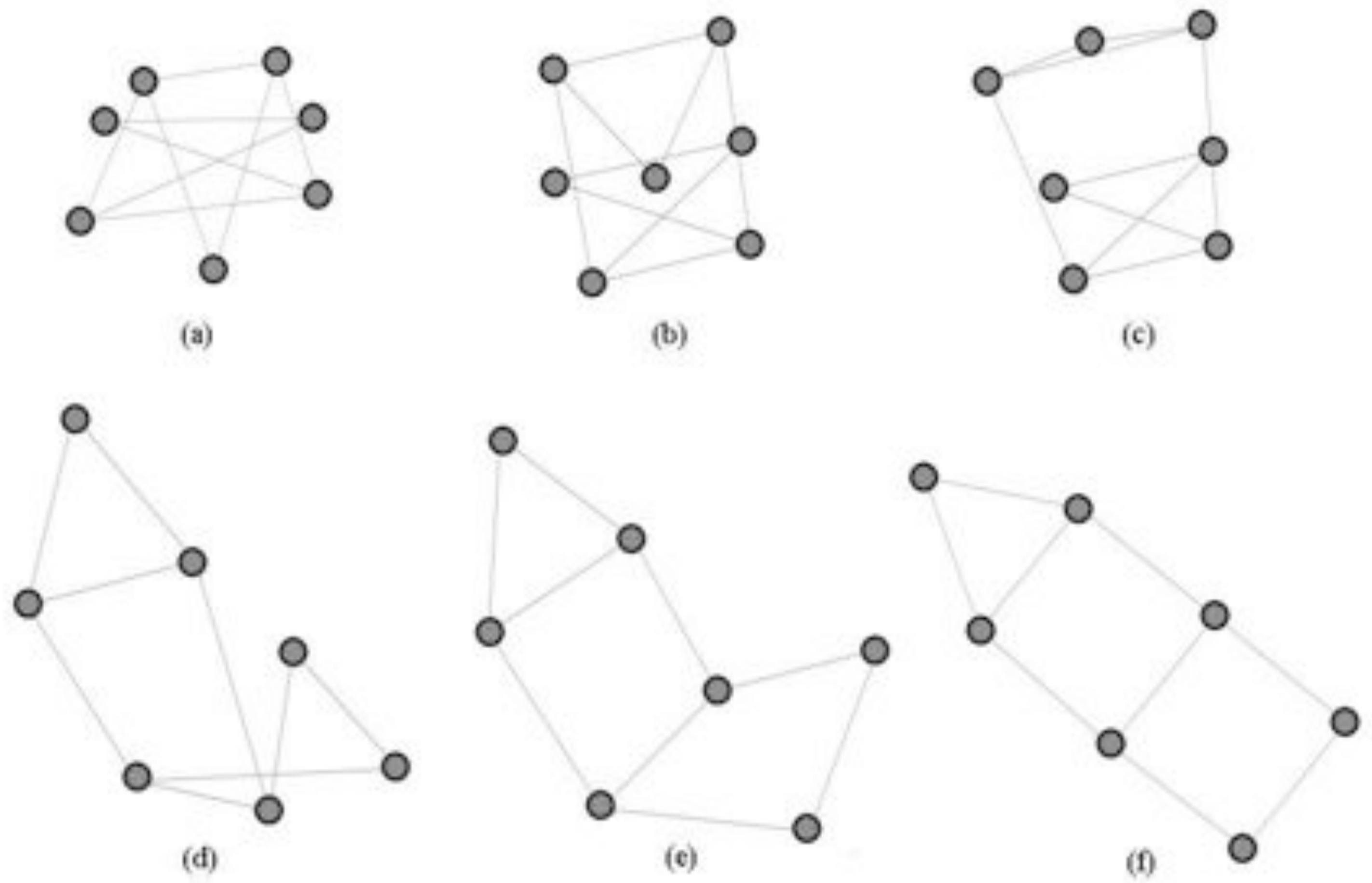
$$F_{ij}^{c} = \frac{Q_{ij}}{|r_i - r_j|^2}$$

either $Q_{ij} = Q$ or, e.g., $Q_{ij} = k_i\, k_j$

Repulsion pulls all nodes apart, springs keep connected nodes together
$\rightarrow$ **workhorse method** for small to medium sized graphs

$\rightarrow$ Do-it-yourself in Assignment 2 <=

Spring-Electrical Example



http://www.it.usyd.edu.au/~aquigley/3dfade/

Force-Directed Layout: Summary

Analogy to a **physical** system
=> force directed layout methods tend to meet various **aesthetic** standards:

- efficient **space filling**,
- **uniform** edge length (with equal weights and repulsions)
- **symmetry**
- smooth **animation** of the layout process (visual continuity)

Force directed graph layout → the "**work horse**" of layout algorithms.

Not so nice: the **initial random placement** of nodes and even very small changes of layout parameters will lead to **different representations**.
(no unique solution)

Side-effect: vertices at the periphery tend to be closer to each other than those in the center…

Runtime Scaling

Force directed layout:

```
loop until convergence:
   calculate forces:
      $L$ springs
      $N(N-1)/2$ charge pairs
   move vertices
   output positions
```

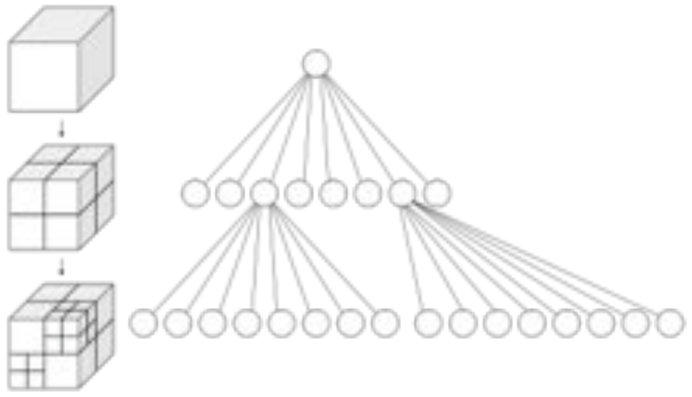
Several possible arrangements!!! (local minima)

$O(N^2)$!!!

→ force directed layout suitable for small to medium graphs (≤ O(1000) nodes?)

Speed up layout by:

- **multi-level** techniques to overcome local minima
- **clustering** (octree) methods for distant groups of nodes → *O(N log N)*



H3 Algorithm

Two problems of force directed layout:

- runtime scaling
- 2D space for drawing the graph

Tamara Munzner (1996-1998): H3 algorithm

→ **interactively** visualize **large data sets** of ~100.000 nodes.

- focusses on **quasi-hierarchical** graphs
  → use a **spanning tree** as the backbone of a layout algorithm
- graph layout in **exponential space** (projected on 2D for interactive viewing)

Spanning tree: connected acyclic subgraph that contains all the vertices of the original graph, but does not have to include all the links

→ find a minimum-weight spanning tree through a graph with weighted edges, where **domain-specific information** is used to compute the **weights**

Spanning Tree

Some algorithms work only/better on trees

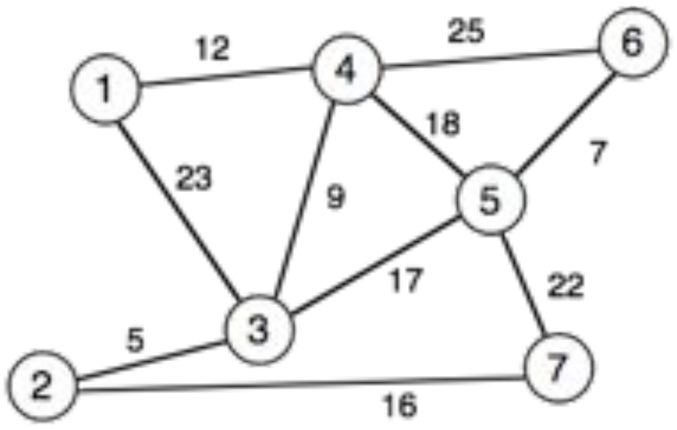
Idea: remove links until graph has tree structure, keep all nodes connected
→ spanning tree

Minimal spanning tree = spanning tree with the least total weight of the edges

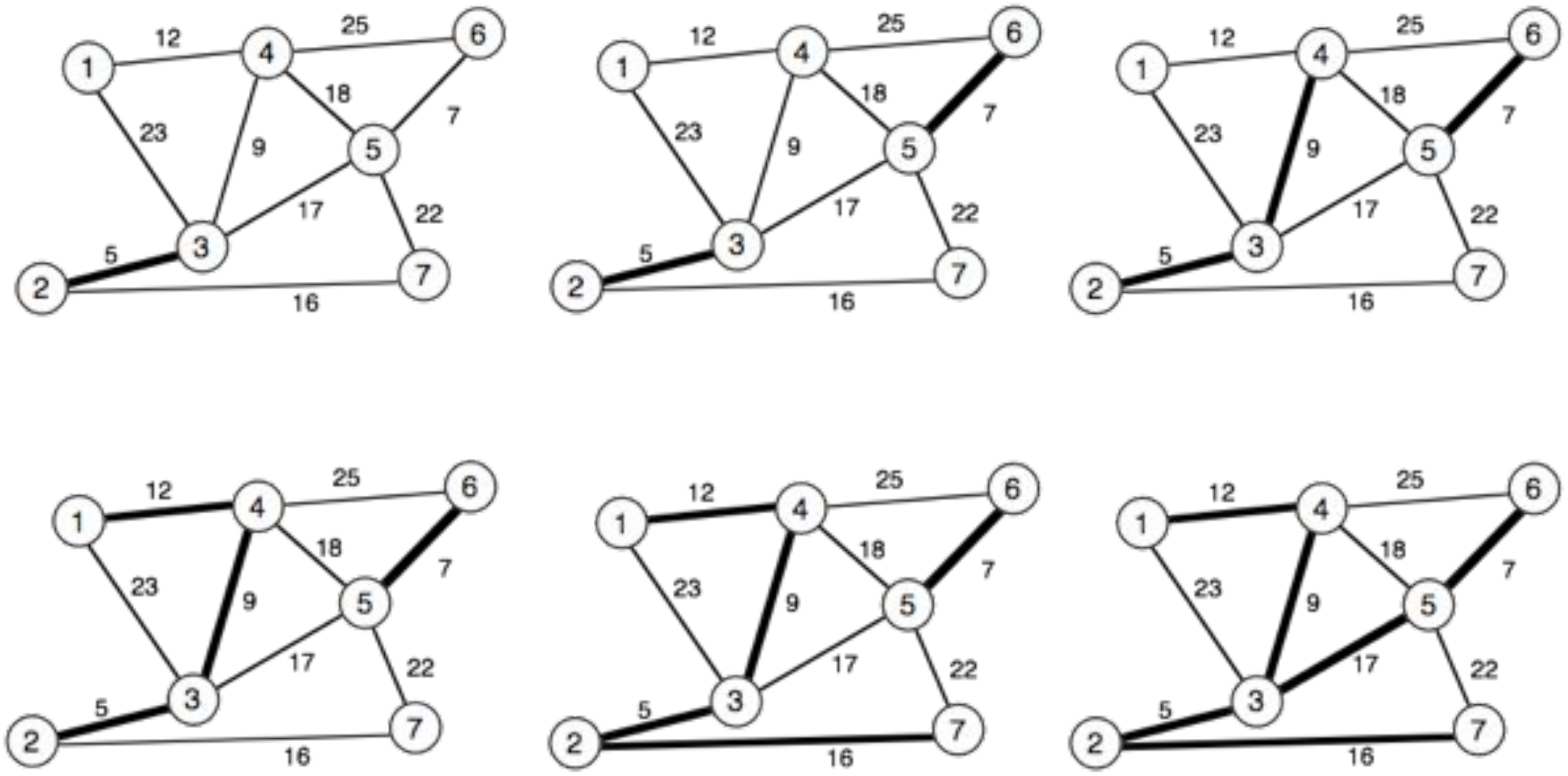
Greedy **Kruskal**-Algorithm:

→ **iteratively** choose unused edge
with **least weight**,
if it does not lead to a **circle**!

greedy <=> base choice on current state,
(locally optimal choice)



Kruskal - Example



Proof that there is no spanning tree with a **lower** weight?

Minimum spanning tree weight = 66

Spanning Tree Construction

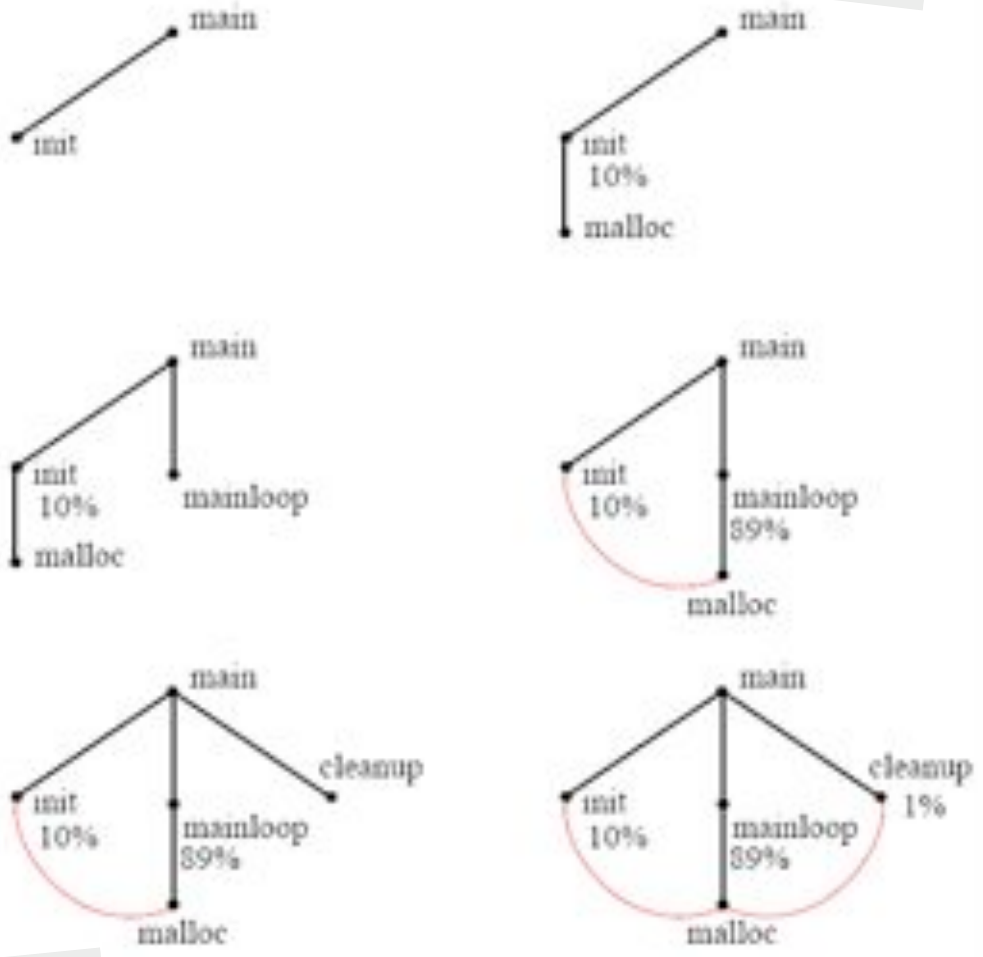
→ Weights for the spanning tree???

Constructing a spanning tree for quasi-hierarchical function call graph.

In this simple hypothetical function call graph, nodes represent functions of a computer code, and links represent calls from one function to another.

The **call graph** is computed by a **static analysis** of the program text. The **spanning tree** is determined by **run-time profiling** of the code so that the calling procedure that is responsible for the **most execution time** in the called procedure is the parent.

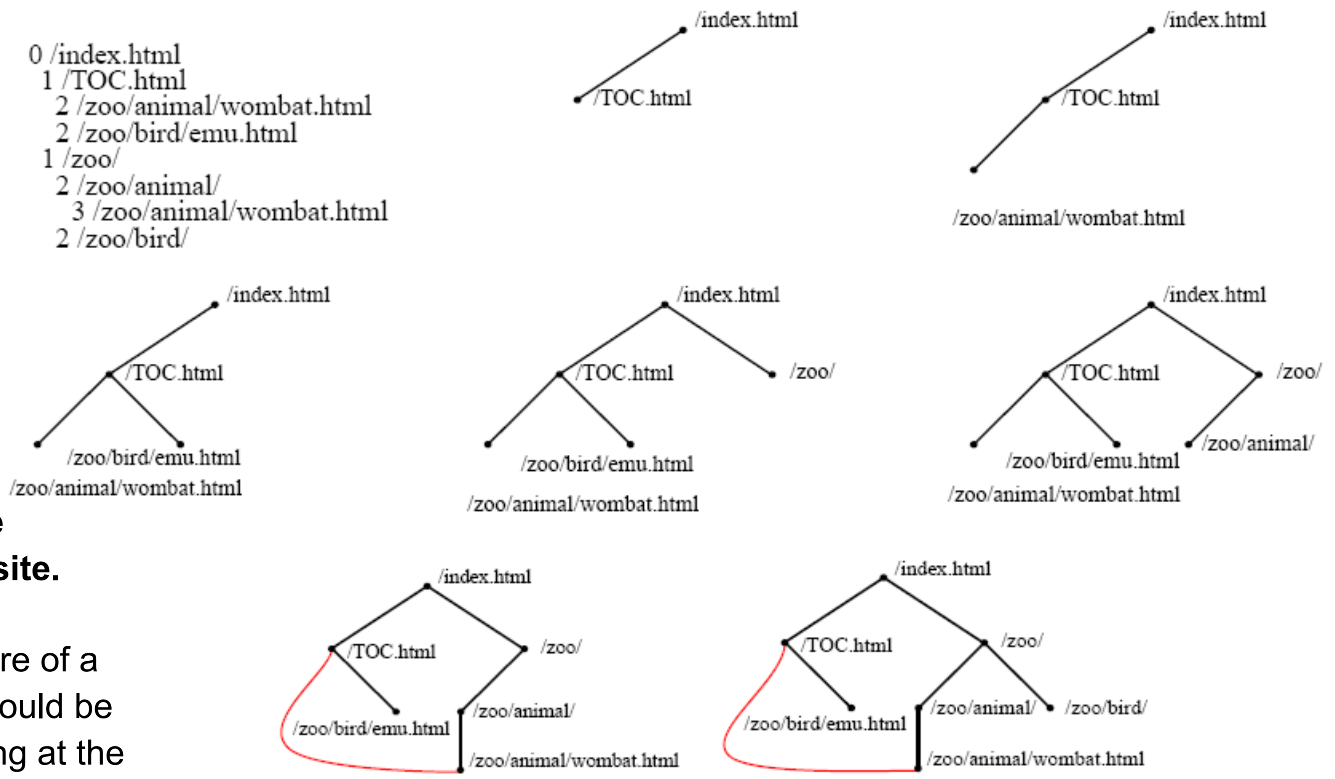
We show the layout incrementally as in the figure before: the parent of a node can change when new information about a more appropriate candidate emerges, and the small multiples should be read row by row starting at the top left



PhD thesis Tamara Munzner, chapter 3

Spanning Tree for a web site

```
0 /index.html
  1 /TOC.html
    2 /zoo/animal/wombat.html
    2 /zoo/bird/emu.html
  1 /zoo/
    2 /zoo/animal/
      3 /zoo/animal/wombat.html
    2 /zoo/bird/
```

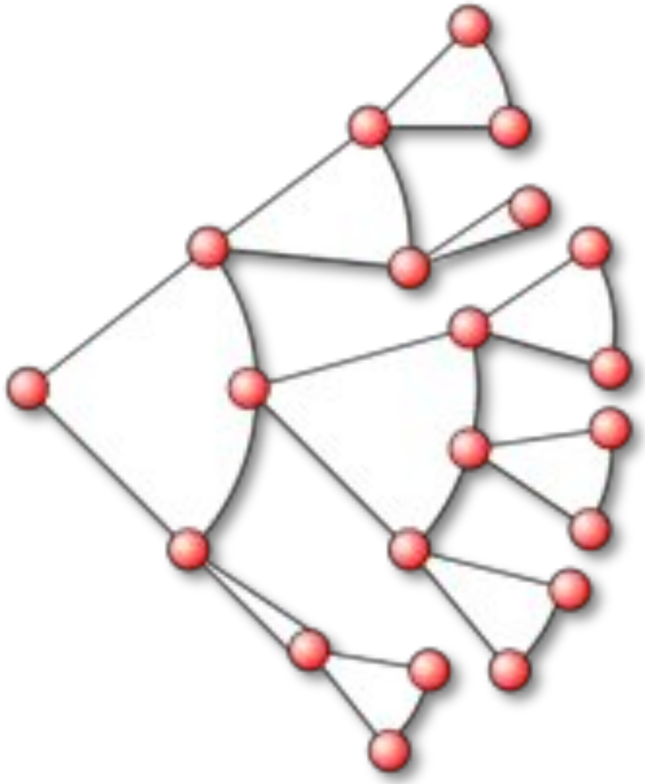


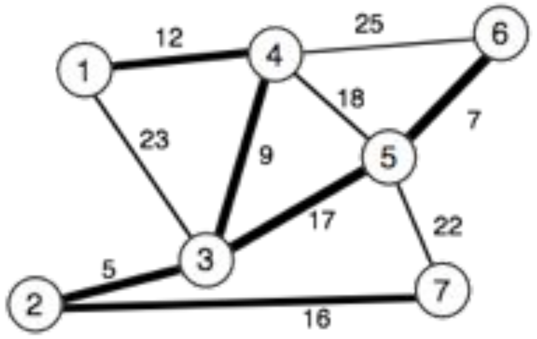
Constructing a spanning tree for a quasi-hierarchical web site.

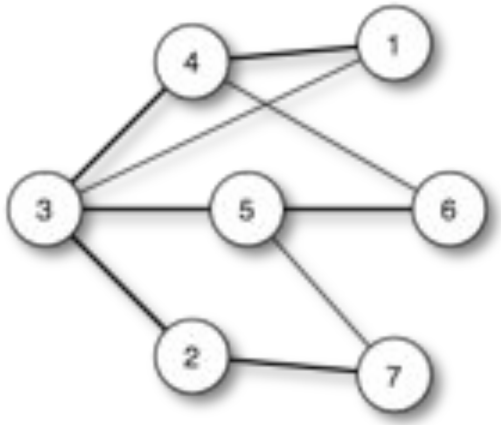
Top Left: The hyperlink structure of a simple hypothetical site, as it would be reported by a web spider starting at the top page. Nodes represent web pages, and links represent hyperlinks. Although the graph structure itself is determined by hyperlinks, additional information about hierarchical directory structure of the site's files is encoded in the URLs.
Top Row: We build up the graph incrementally, one link at a time.
Middle Row: We continue adding nodes without moving any of the old ones around.
Bottom Row: When the `animal/wombat.html` page is added, the label matching test shows that `animal` is a more appropriate parent than `/TOC.html`, so the node moves and the link between `animal/wombat.html` and `/TOC.html` becomes a non-tree link. In the final stage, note that `bird/emu.html` does not move when the `bird` is added, even though the labels match, because there is no hyperlink between them.

Cone Layout

Place the nodes according to their hierarchy
starting from the root node
→ direction indicates lineage







For arbitrary graphs
→ how to get weights?
→ which node is the root?

Exponential Room

In Euklidian space: circumference of a circle grows linear:

$$U = 2\pi r$$

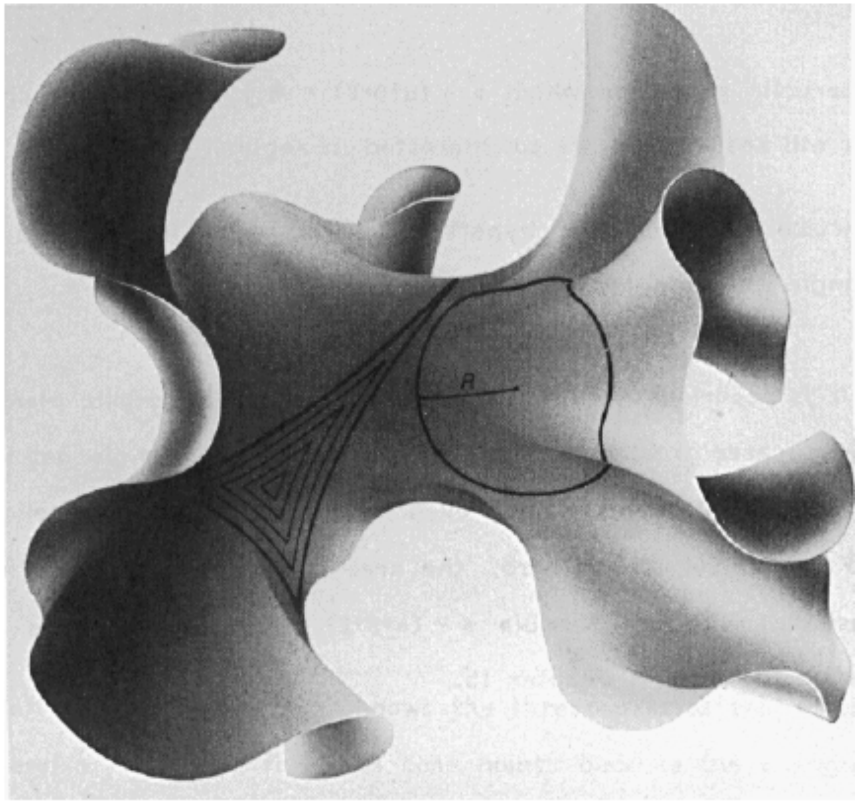
In hyperbolic space:

$$U = 2\pi \sinh r$$

→ exponentially **growing** space
on the circle

For (cone) graph layout
→ there is **enough room**
for yet another level

Also: **mappings** of the
complete hyperbolic space
→ finite volume of Euklidian space



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Models of hyperbolic space

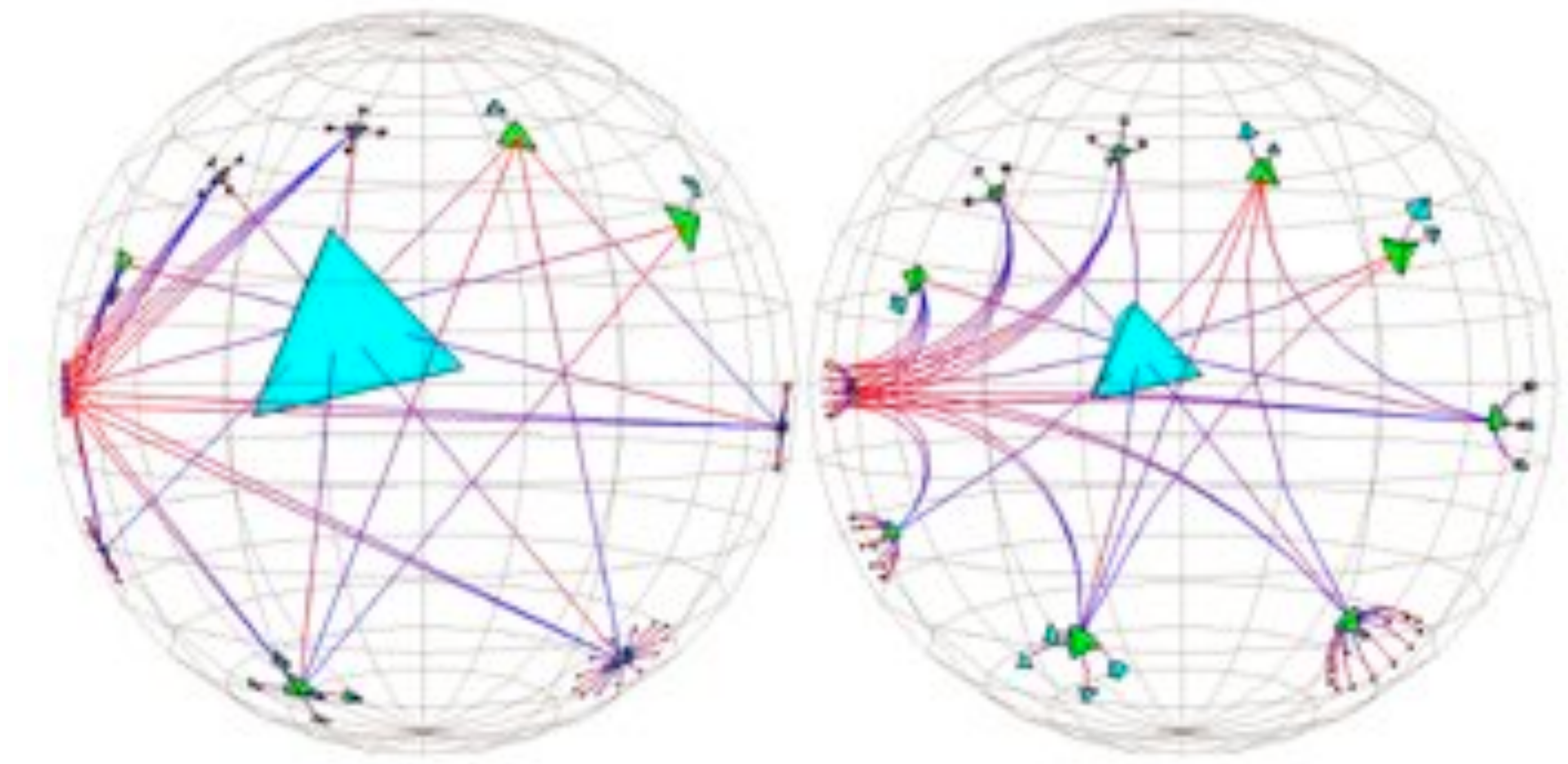

Figure 3.5: **Models of hyperbolic space. Left:** The projective model of hyperbolic space, which keeps lines straight but distorts angles. **Right:** The conformal model of hyperbolic space, which preserves angles but maps straight lines to circular arcs. These images were created with the *webviz* system from the Geometry Center [MB95], a first attempt to extend cone tree layouts to 3D hyperbolic space that had low information density. The cone angle has been widened to 180°, resulting in flat discs that are obvious in the projective view. The arcs visible in conformal view are actually distorted straight lines.

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Visualization with H3

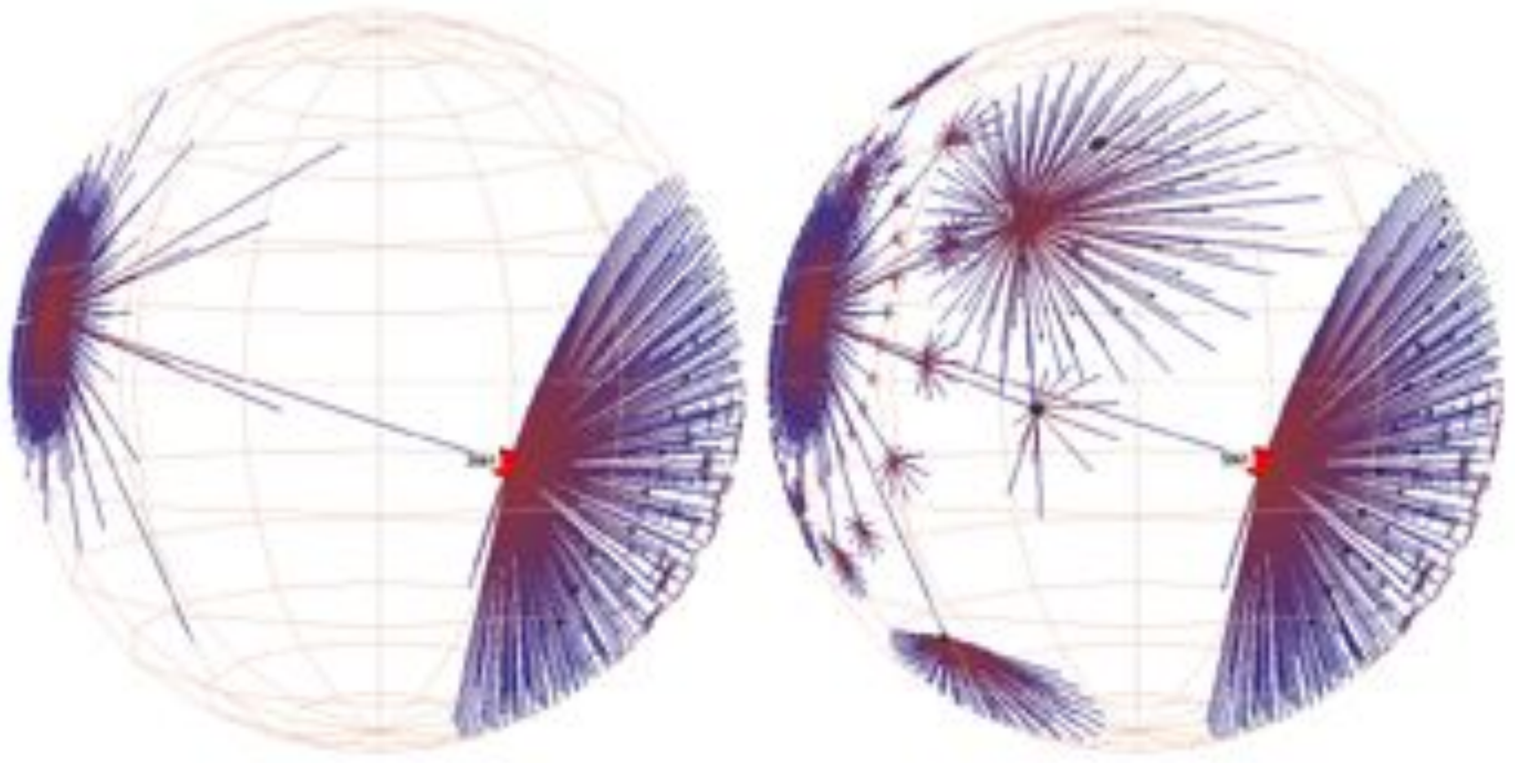

Figure 3.13: **Active vs. idle frames, obvious case.** The H3Viewer guaranteed frame rate mechanism ensures interactive response for large graphs, even on slow machines. **Left:** A frame drawn in 1/20th of a second during user interaction. **Right:** A frame filled in by the idle callbacks for a total of 2 seconds after user activity stopped. The graph shows the peering relationships between Autonomous Systems, which constitute the backbone of the Internet.[8] The 3000 routers shown here are connected by over 10,000 edges in the full graph.

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Visualization with H3

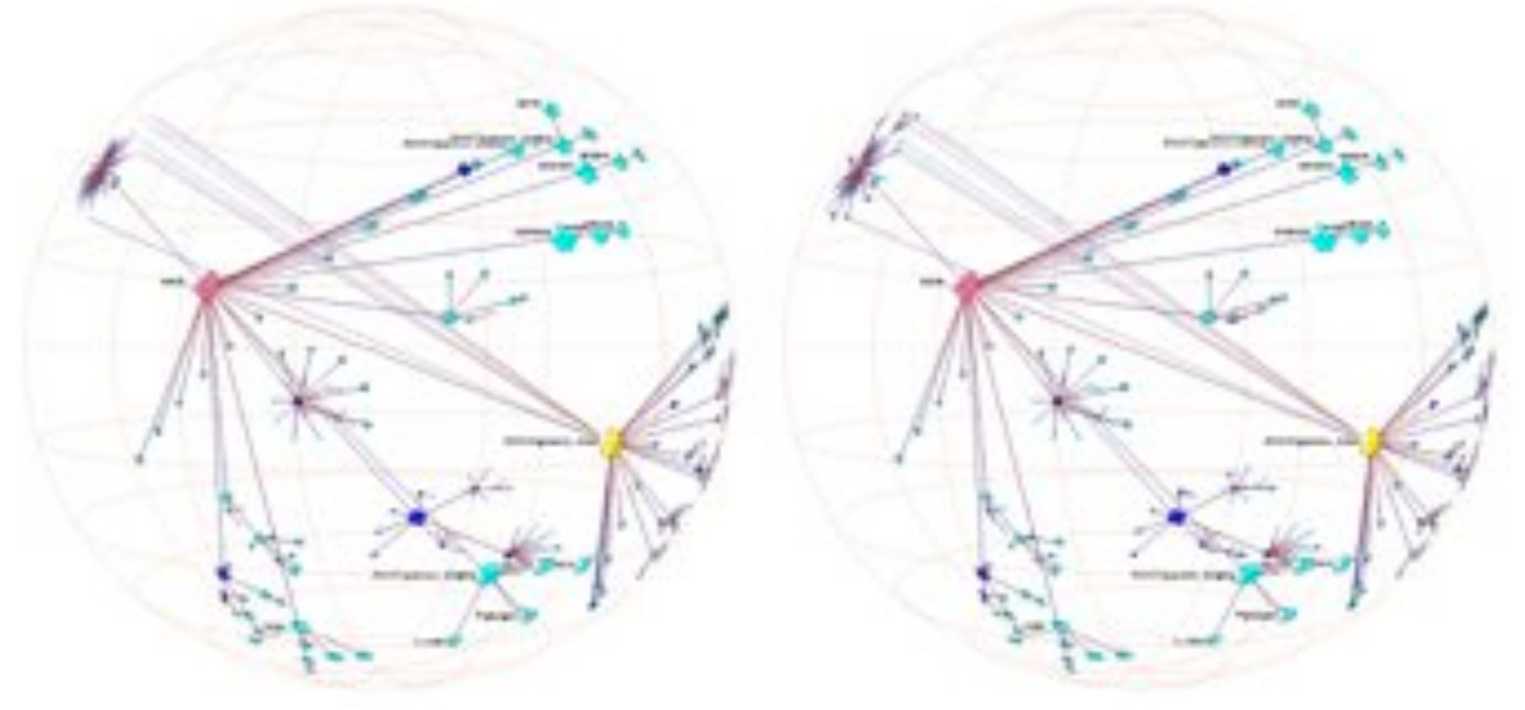

Figure 3.14: **Active vs. idle frames, subtle case.** A function call graph of a small FORTRAN benchmark with 1000 nodes and 4000 edges. Non-tree links from one of the functions are drawn. **Left**: a single frame has been drawn in 1/20th of a second. Note that the non-tree links to the distant fringe are visible even though their terminating nodes were small enough that the active drawing loop terminated before they could be drawn. Our drawing algorithm thus hints at the presence of potentially interesting places that the user might wish to drag toward the center to see in more detail. **Right**: The entire graph is drawn after the user has stopped moving the mouse. The graph is small enough that the difference between the two frames is more subtle than in Figure 3.13, and is visible only in the fringe in the upper left corner.

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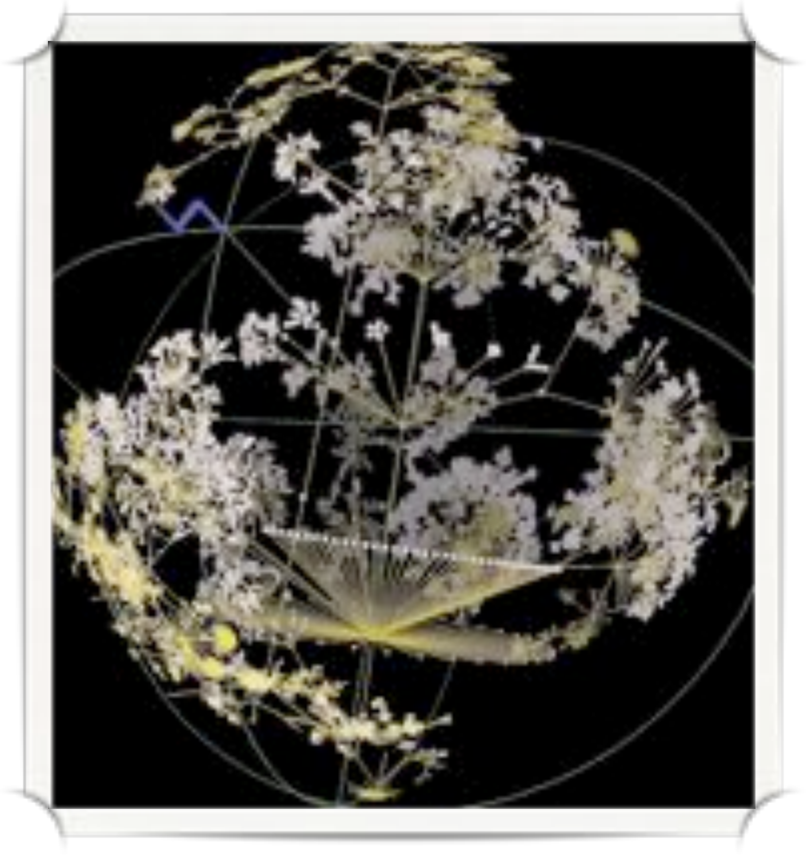
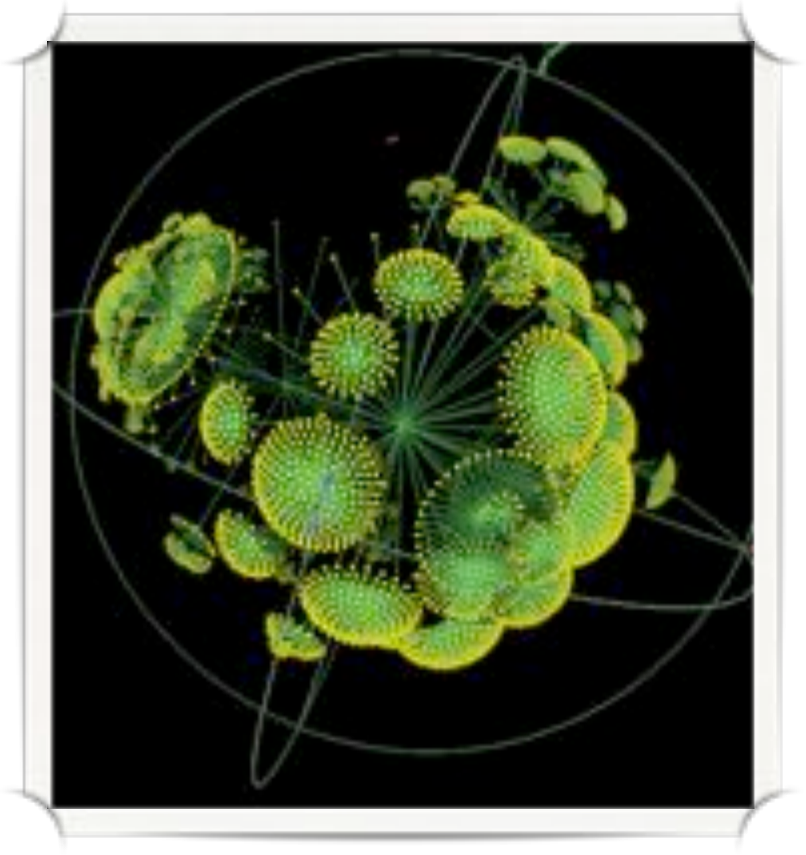
GIFs don't work here…





http://www.caida.org/tools/visualization/walrus/gallery1/

H3: + layout based on MST → fast
+ layout in hyperbolic space → enough room
– how to get the MST for biological graphs????

Summary

What you learned **today**:

→ Local connectivity: clustering

→ shortest path: Dijkstra algorithm

→ graph layout: force-directed and embedding schemes

→ spanning tree: Kruskal algorithm

Next lecture:

→ biological data to build networks from