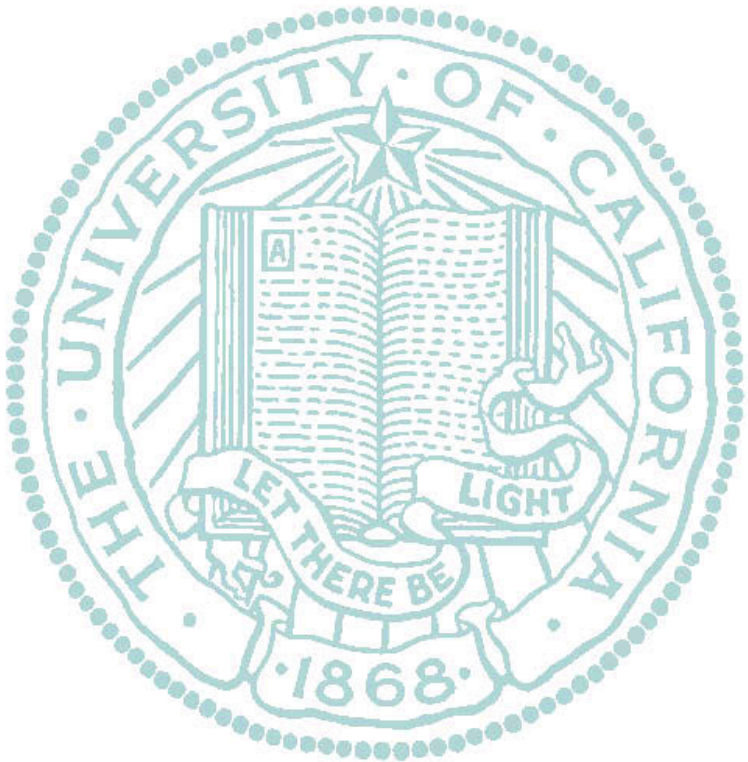
BMI-203: Biocomputing Algorithms
Lecture 2: Graphs, Trees, and Searching



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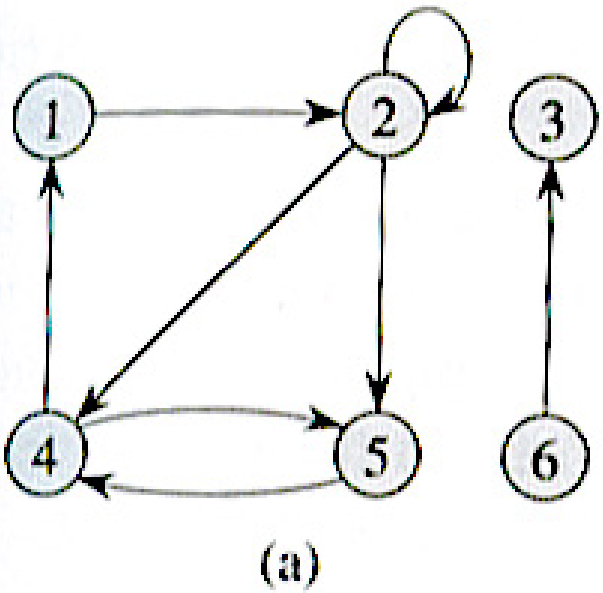
Outline

- Graphs, Trees, Search (see Cormen, 5.4–5.5, Chapter 13, Chapters 23–24, 27)
  - Many different interesting algorithms in Bioinformatics use graphs as representations
- Homework: An algorithm for computing the minimum rmsd of two molecules under graph equivalences
- Reference: Introduction to Algorithms, Second Edition by Thomas H. Cormen (Editor), Charles E. Leiserson, Ronald L. Rivest

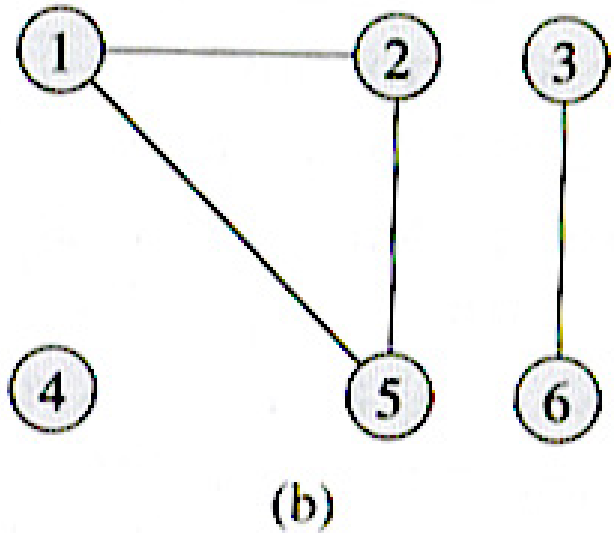
What is a graph?

- A **directed graph** *G* is a pair *(V, E)* where *V* is a finite set and *E* is a binary relation on *V*
- *V* is the **vertex set**
- *E* is the **edge set**
  - Set of *(u, v)* where *u,v* are in *V*
- Graphs can be **directed** or **undirected**
- Degree: number of edges connected to a vertex
- Cycle: path of length greater than 2 which starts and ends on the same vertex

Types of graphs

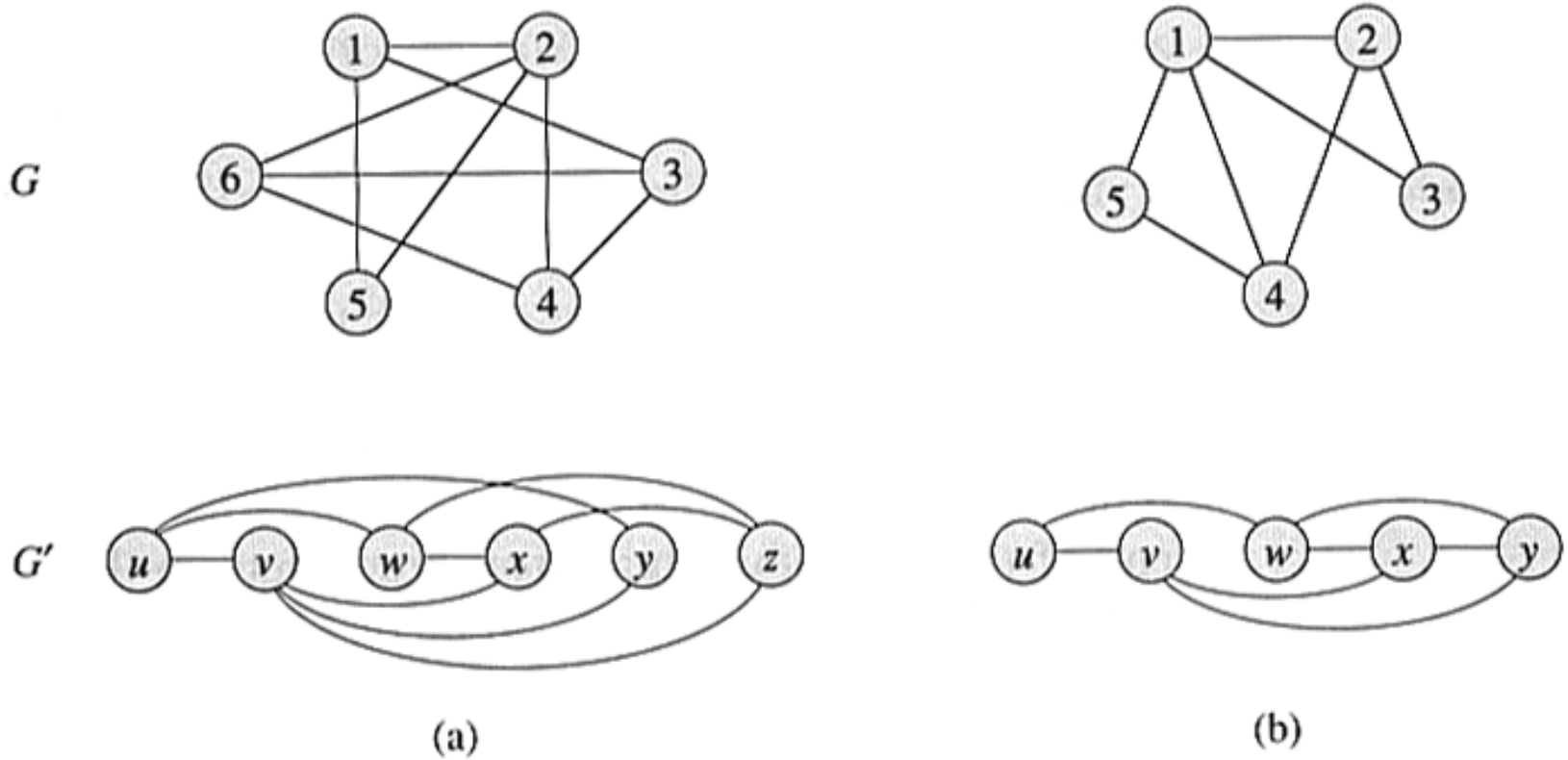


Directed



Undirected

Types of graphs



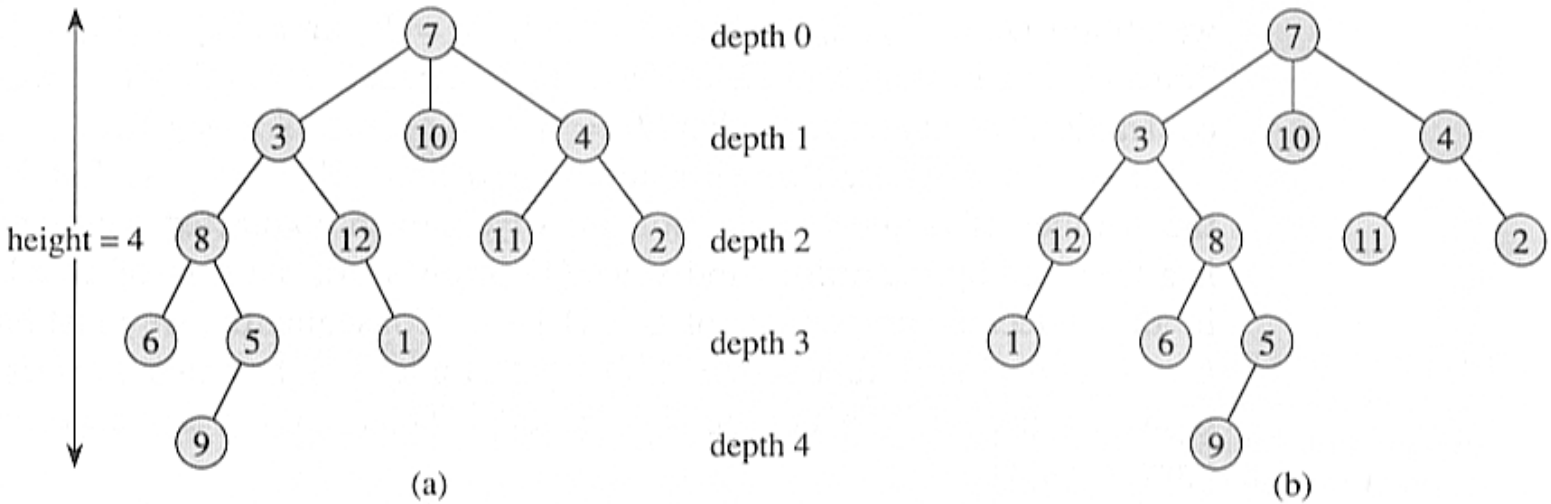
Isomorphic

1,2,3,4,5,6 = u,v,w,x,y,z

Non-isomorphic

What is a tree?

- A tree is an **undirected graph** that is **connected**
- A **rooted tree** is one that has a specified special vertex called the **root**
- Trees can be **ordered** or not

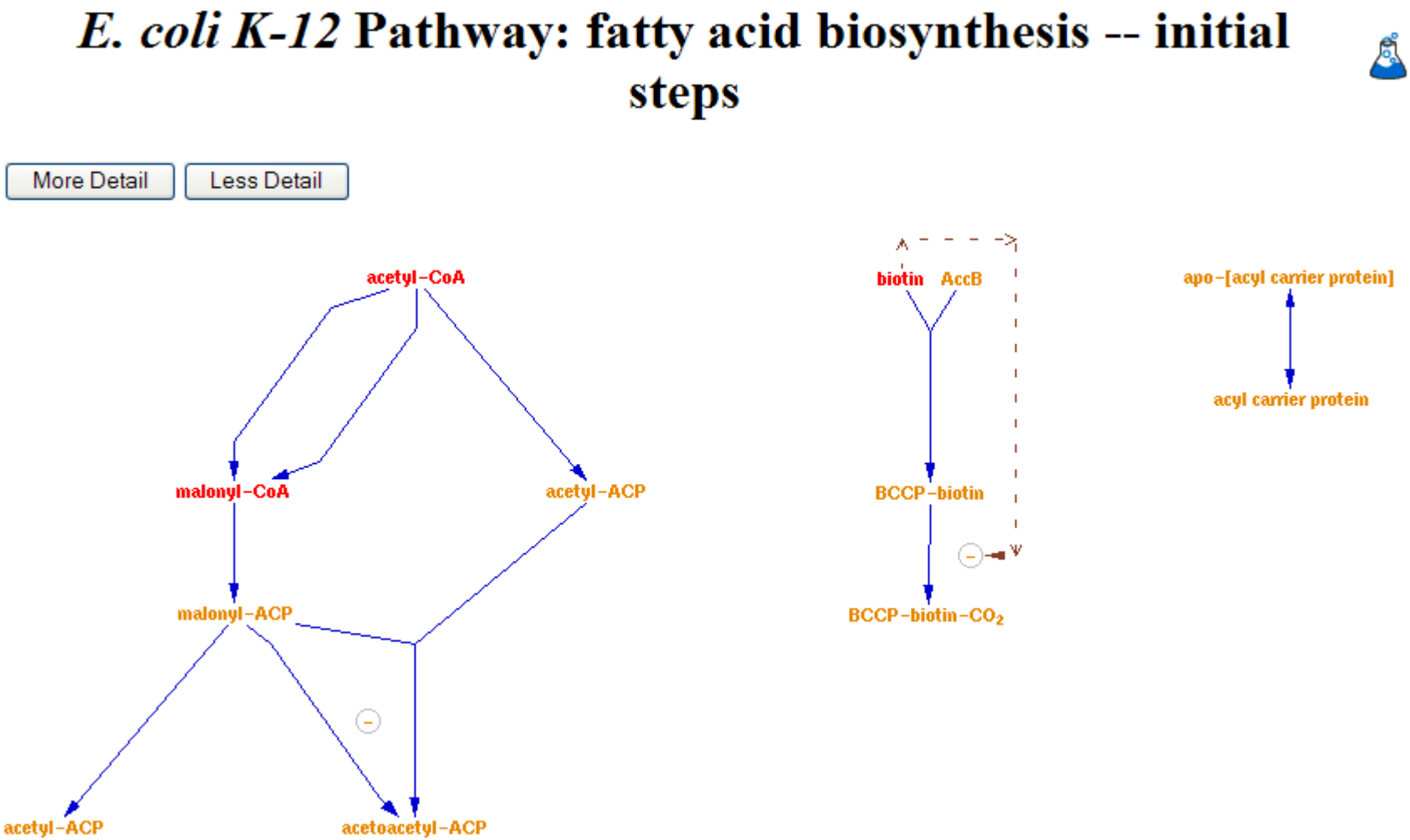


Graphs in bioinformatics: Can represent many things

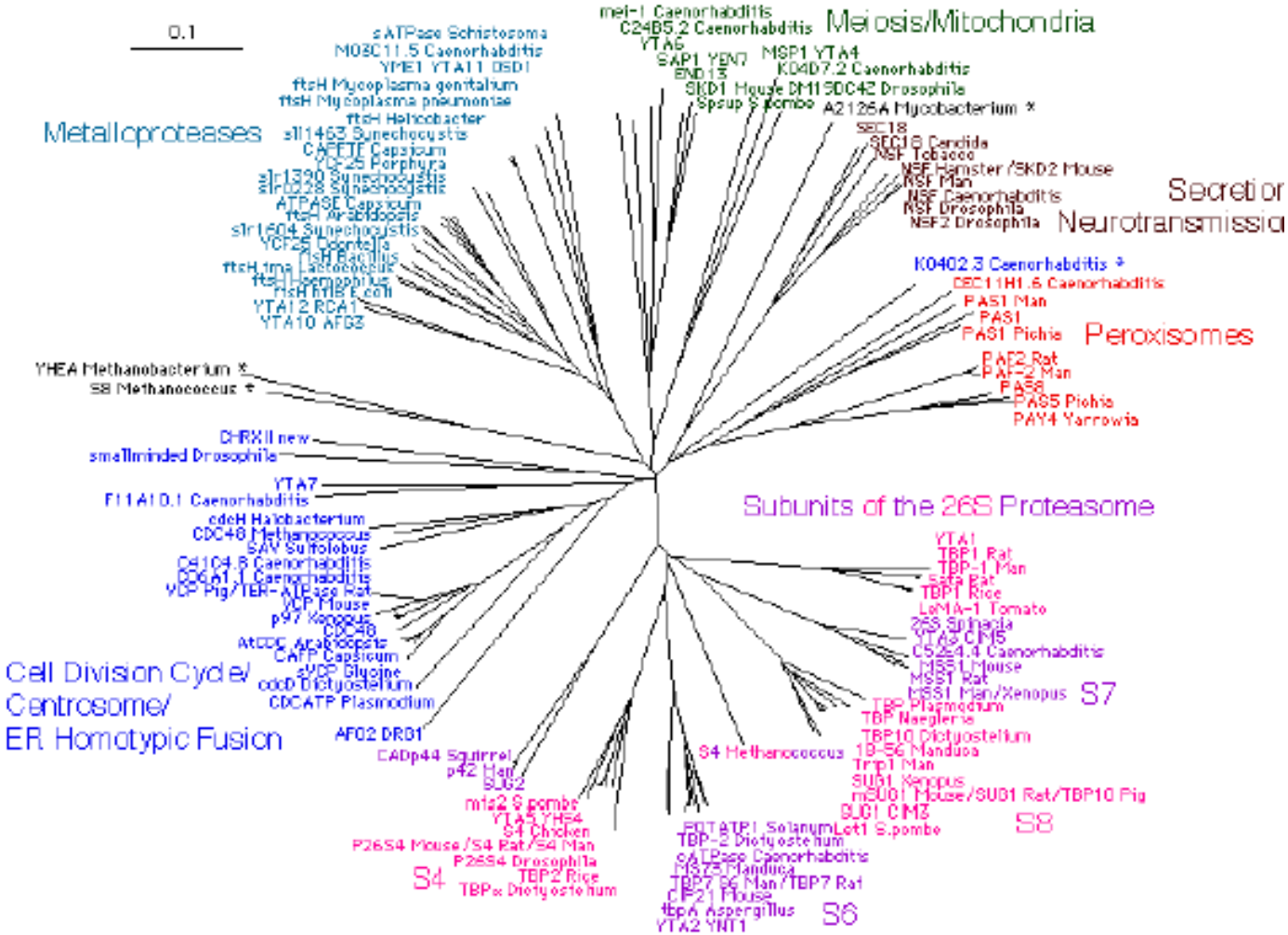
- Molecules
  - Proteins and DNA: connected, acyclic, directed graphs
  - Organic molecules: connected, possibly cyclic, undirected graphs

Blackboard Examples

Graphs in bioinformatics: Metabolic Pathways (EcoCyc)

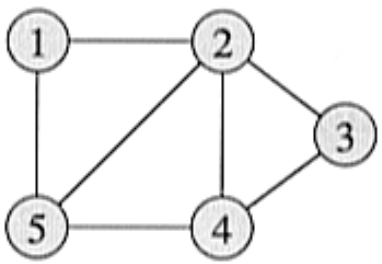


Graphs in bioinformatics: Phylogenetic trees

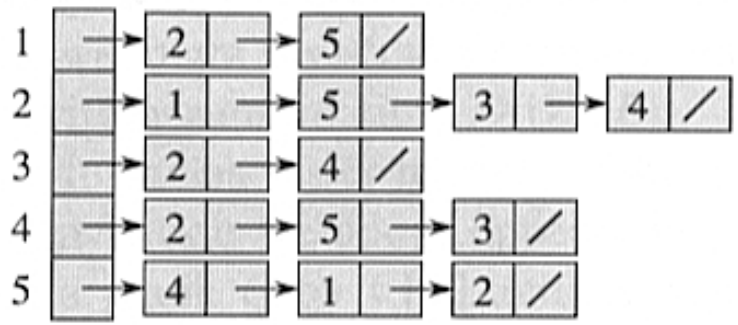


Representing graphs

- Adjacency list
- Adjacency matrix



(a)



(b)

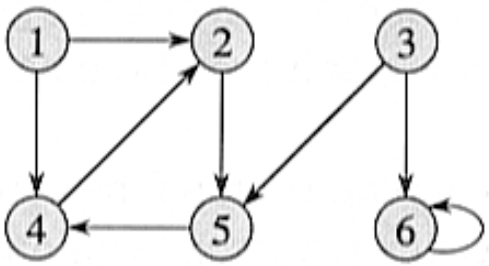
	1	2	3	4	5
1	0	1	0	0	1
2	1	0	1	1	1
3	0	1	0	1	0
4	0	1	1	0	1
5	1	1	0	1	0

(c)

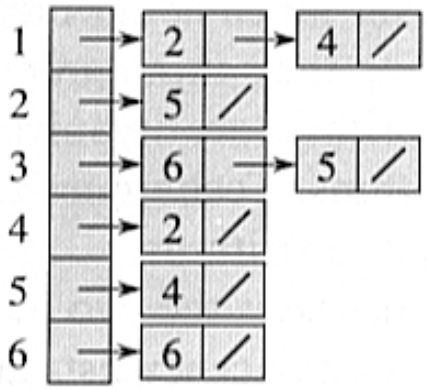
Undirected graph: Matrix is symmetric

Representing graphs

- Adjacency list
- Adjacency matrix



(a)



(b)

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

(c)

Directed graph: Matrix is asymmetric

Traversing graphs

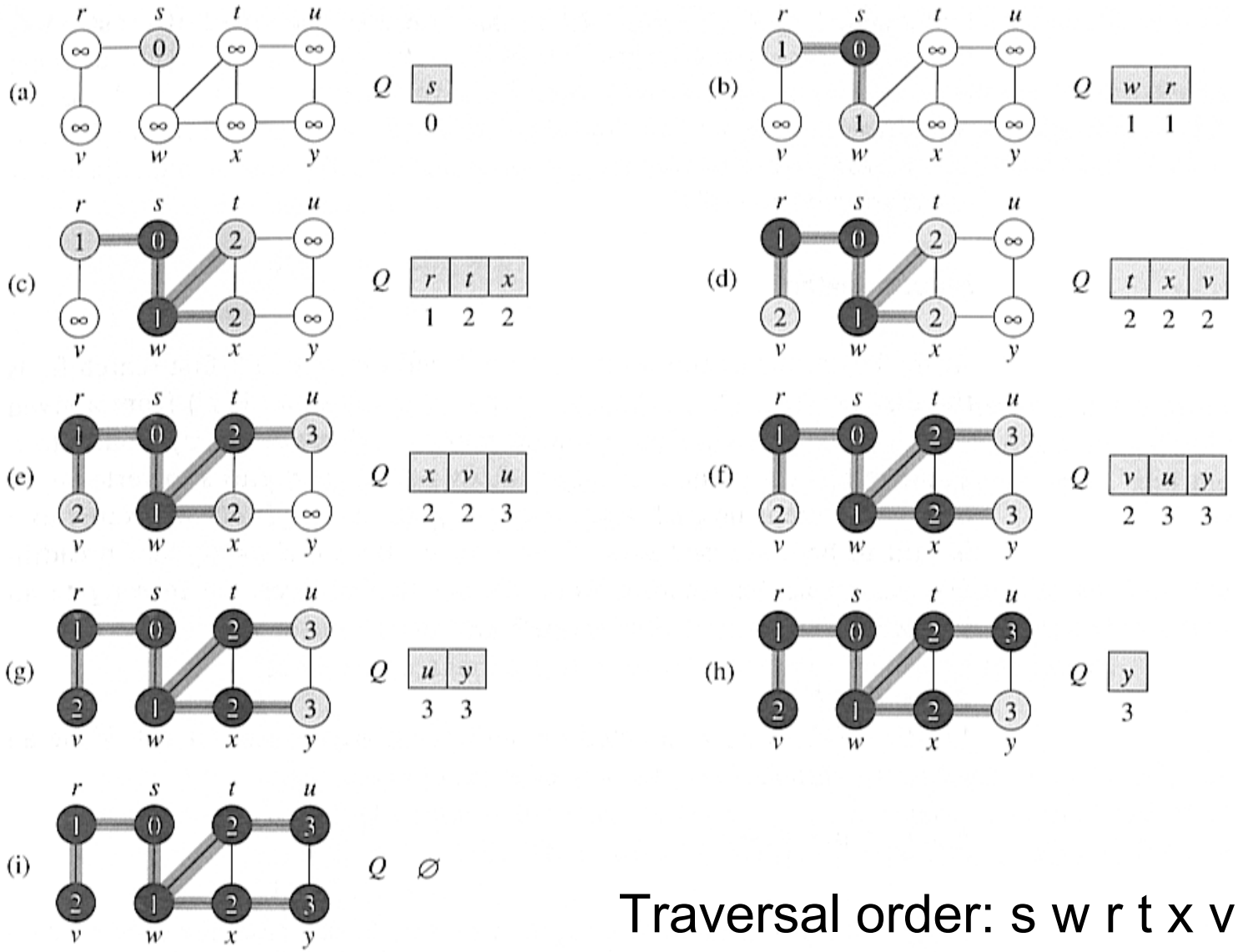
- Two basic strategies
  - Breadth first
    - We traverse all of the connected vertices of our current vertex
    - Stop when we run out of vertices
  - Depth first
    - We traverse the first untraversed vertex connected to our current vertex *and recursively down*
    - Stop when we run out of vertices

Breadth first search

- We start with all vertices initialized:
  - White
  - Depth infinite
  - Predecessor NULL
- We queue up vertices before traversing them

```
for each vertex u
        intialize values
                d <– infinity
                color <– white
                pred <– null
mark start vertex s (0, white, null)
enqueue (q,s)
while q is non-null
        u <– head(q)
                for each connected v
                        if white
                                mark gray
                                d(v) = d(u) + 1
                                pred(v) = u
                                enqueue(q,v)
                dequeue(q)
                color(u) <– black
```

Breadth first search



Traversal order: s w r t x v u y

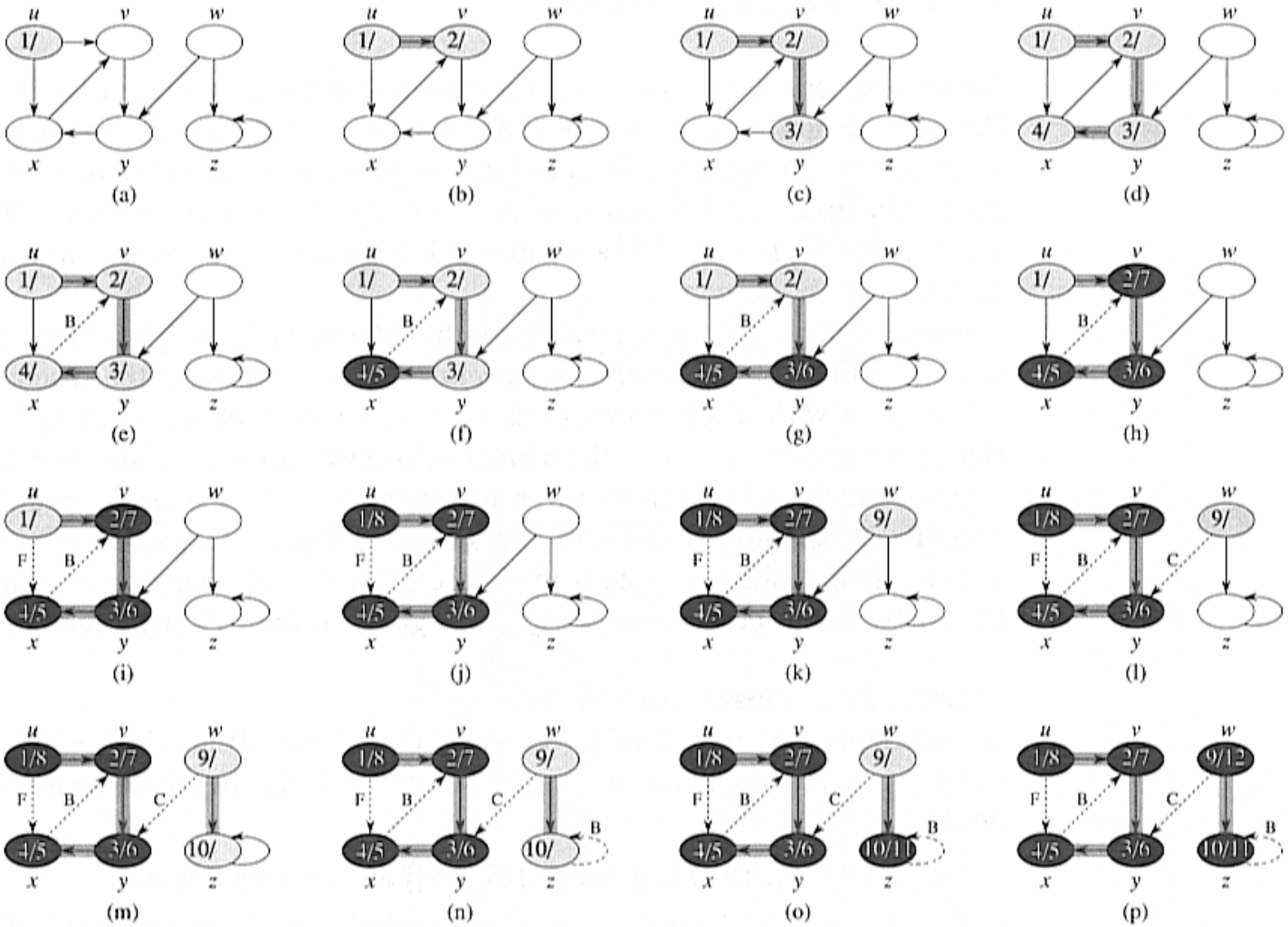
Depth first search

- We start with all vertices initialized:
  - White
  - Time 0
  - Predecessor NULL
- We recursively traverse downward, processing the vertices as we go

```
dfs(g)
time <– 0
for each vertex u
        intialize values
                d <– 0
                color <– white
                pred <– null
for each vertex u
        if (color(u) is white) dfs-visit(u)

dfs-visit(u)
color(u) <– gray
time <– time+1
d(u) <– time
for each v adjacent to u
        if white
                pred(v) = u
                dfs-visit(v)
color(u) <– black
time <– time+1
finish(u) <– time
```

Depth first search



Traversal order: u v y x (back up) w z (back up)

BFS and DFS form the basis of other algorithms

- Finding a cycle:
  - Do a depth first search
  - If, as we are traversing, we encounter a vertex that we have already marked gray, we have a cycle
- Are two atoms (A,B) part of a ring system?
  - Break their bond (edge)
  - Perform DFS from atom A
  - If we encounter atom B, they are part of a ring system

Other operations on graphs

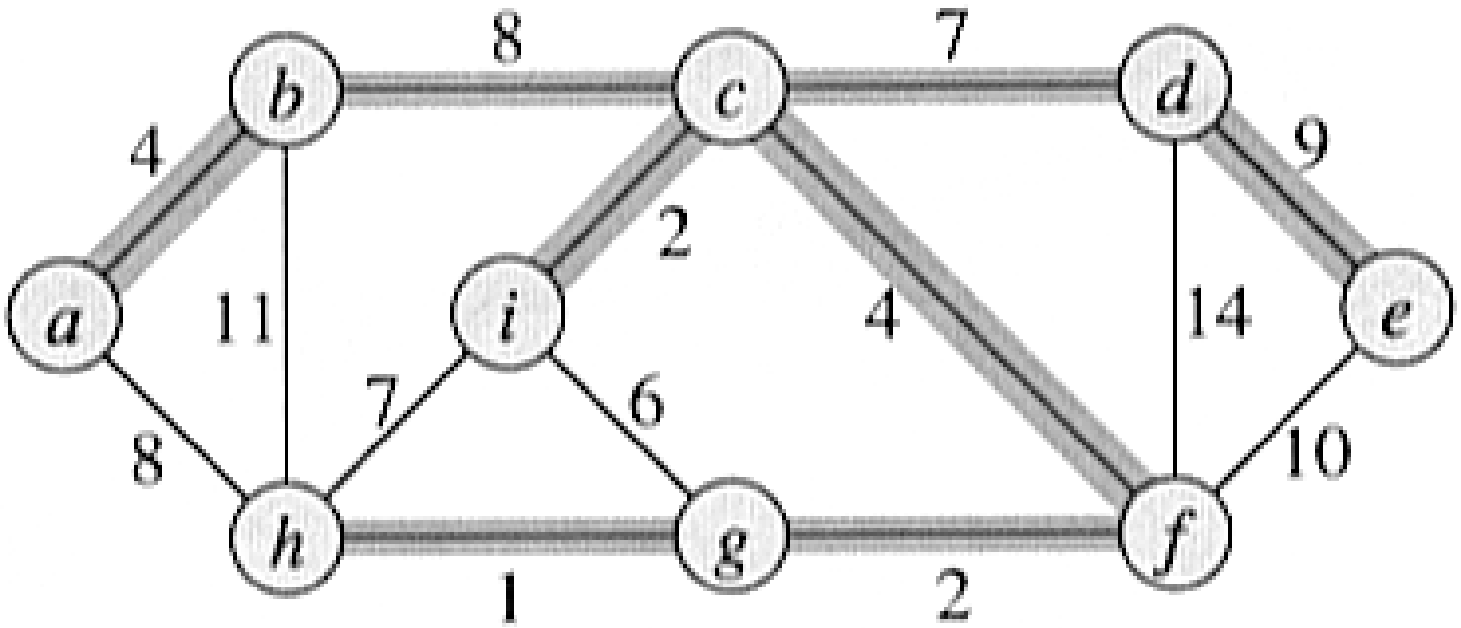
- Minimum spanning trees
  - Can be applied to clustering
  - Interesting applications in many fields (electronic circuit design, molecular diversity)
- Flow
  - Obvious applications in metabolic network analysis

Minimum spanning trees

- You have a weighted, connected, undirected graph G

- You must find the tree T such that
  - T is a subgraph of G
  - T spans all vertices of G
  - The total edge weight of T is a minimum

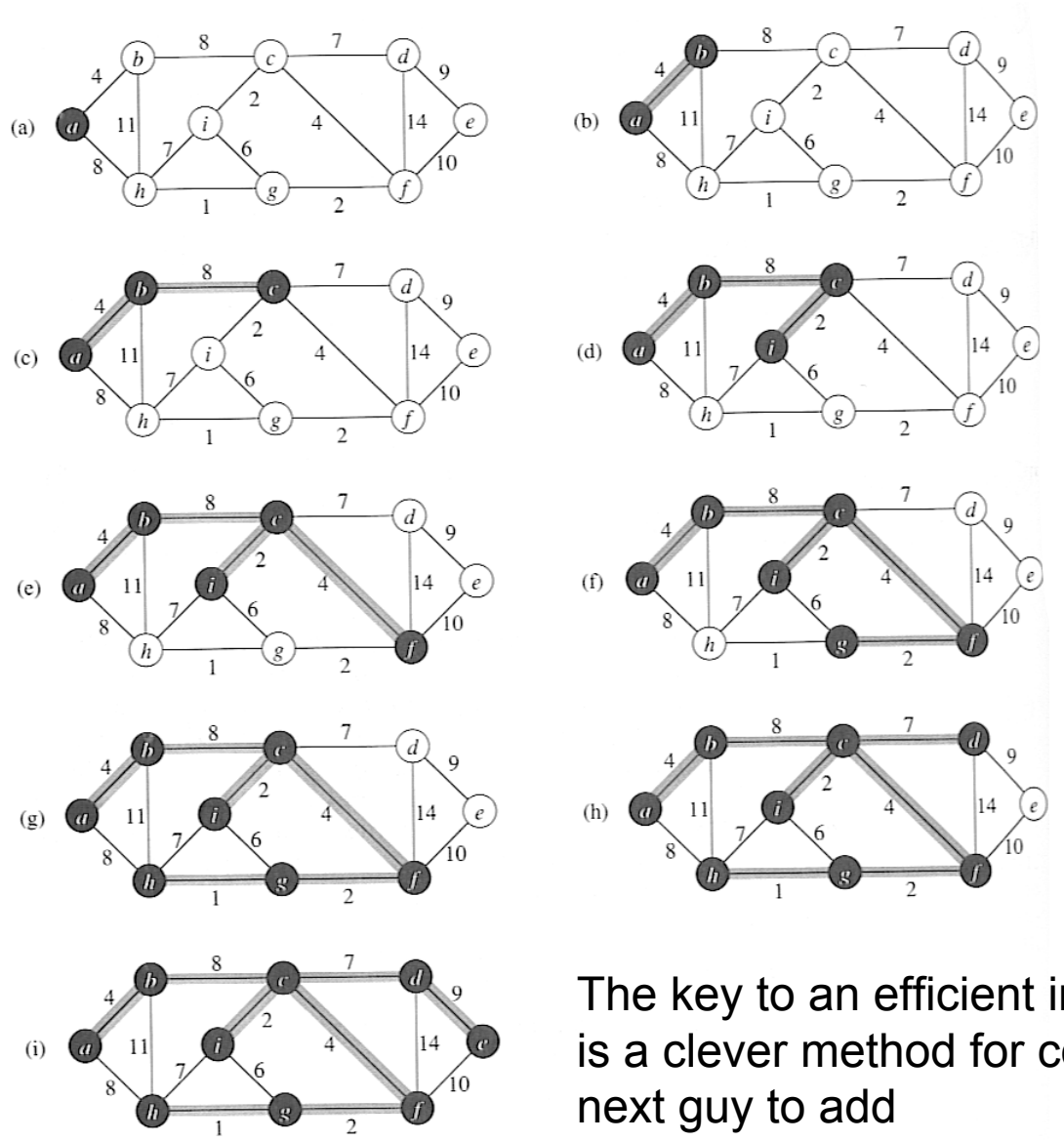
Minimum spanning tree



We will use a **greedy** algorithm

- We will grow a tree while maintaining the invariant that the tree *must be* a minimum spanning tree
- We start with any vertex, since all vertices must eventually be part of the tree
- We add vertices cleverly (using *safe* edges), to make sure we end up with a tree and that the tree is minimal
- The proof is by induction (see pages 500–502 in Algorithms)

Prim's algorithm: Pictorially

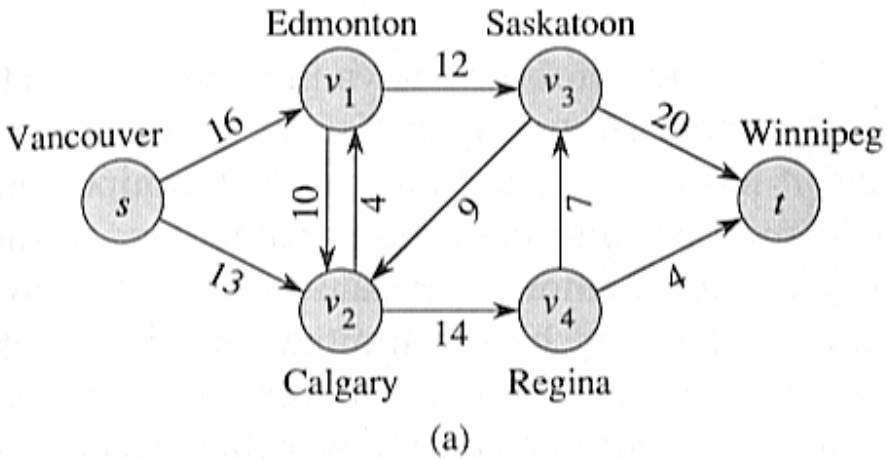


The key to an efficient implementation is a clever method for computing the next guy to add

Maximum Flow

- A flow network is a directed graph with capacities on the edges
- We define a source and a sink
- A flow is subject to constraints
  - Capacity
  - Conservation
  - Symmetry

Maximum Flow

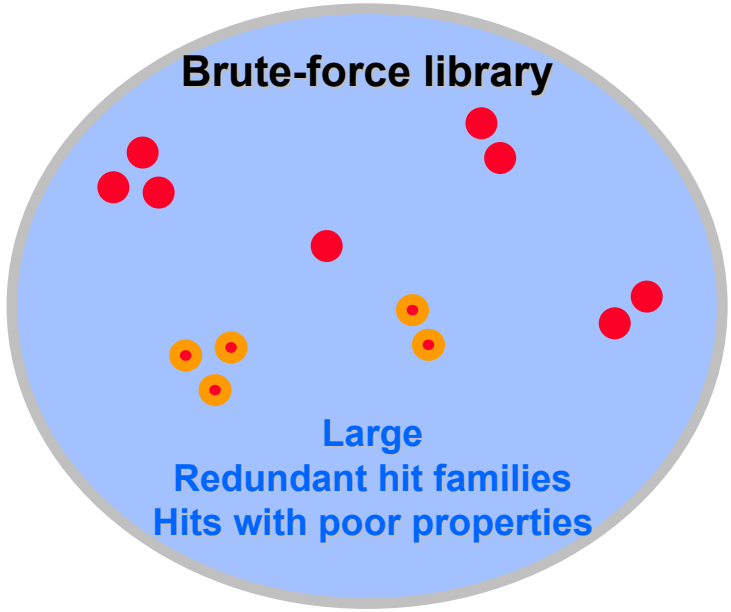


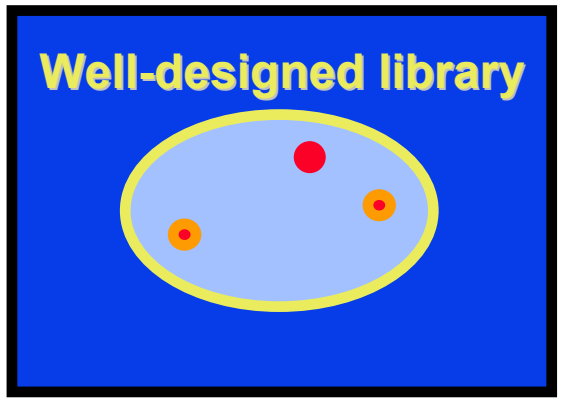
Graphs, trees, and molecules

- Many interesting scientific problems in computational chemistry can be addressed using graph and tree algorithms
  - Molecular diversity
    - We want to pick a small number of molecules from a large collection, where the small set is “diverse”
  - Evaluating the quality of molecular docking
    - We need to compute how good a molecular docking is, but internal symmetries in small molecules makes this nontrivial

Biologically Relevant Chemical Diversity

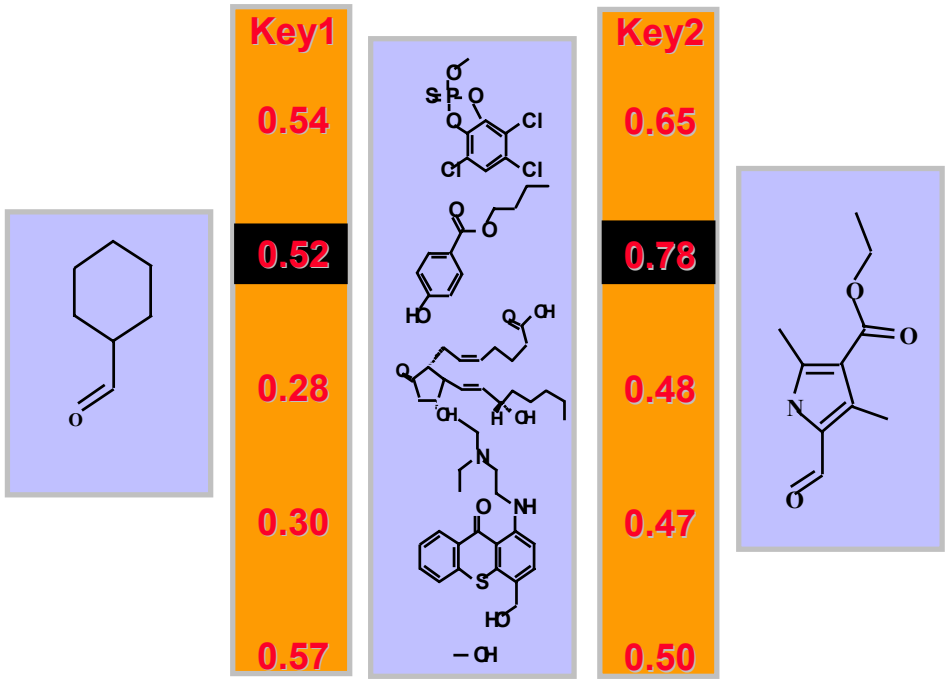
- Diversity increases leverage
  - Smaller number of compounds synthesized
  - Greater number of hits
  - Broader SAR
- Diversity measure must be sensitive to molecular properties that relate to specific binding events
  - **Maximize the likelihood of each molecule probing a different protein binding pocket**
- Critical features of distance measure between molecules
  - **Small distance --> high probability of binding to the same pocket**
  - **Large distance --> low probability of binding to the same pocket**
  - Must be very fast to compute

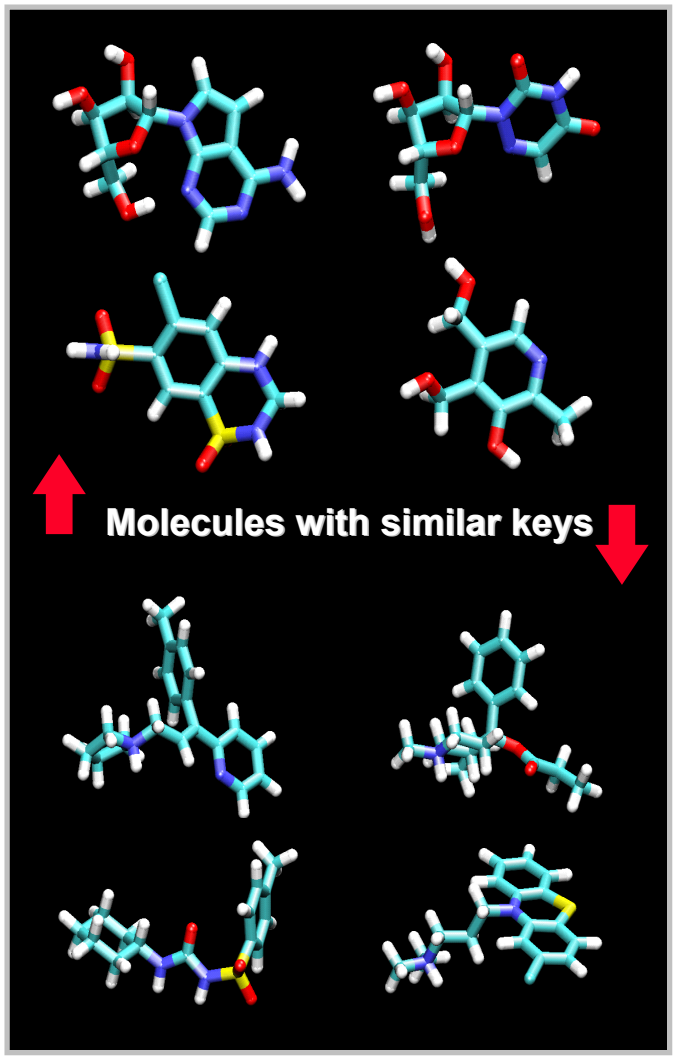




We can compute similarities quickly using vectorial approximations

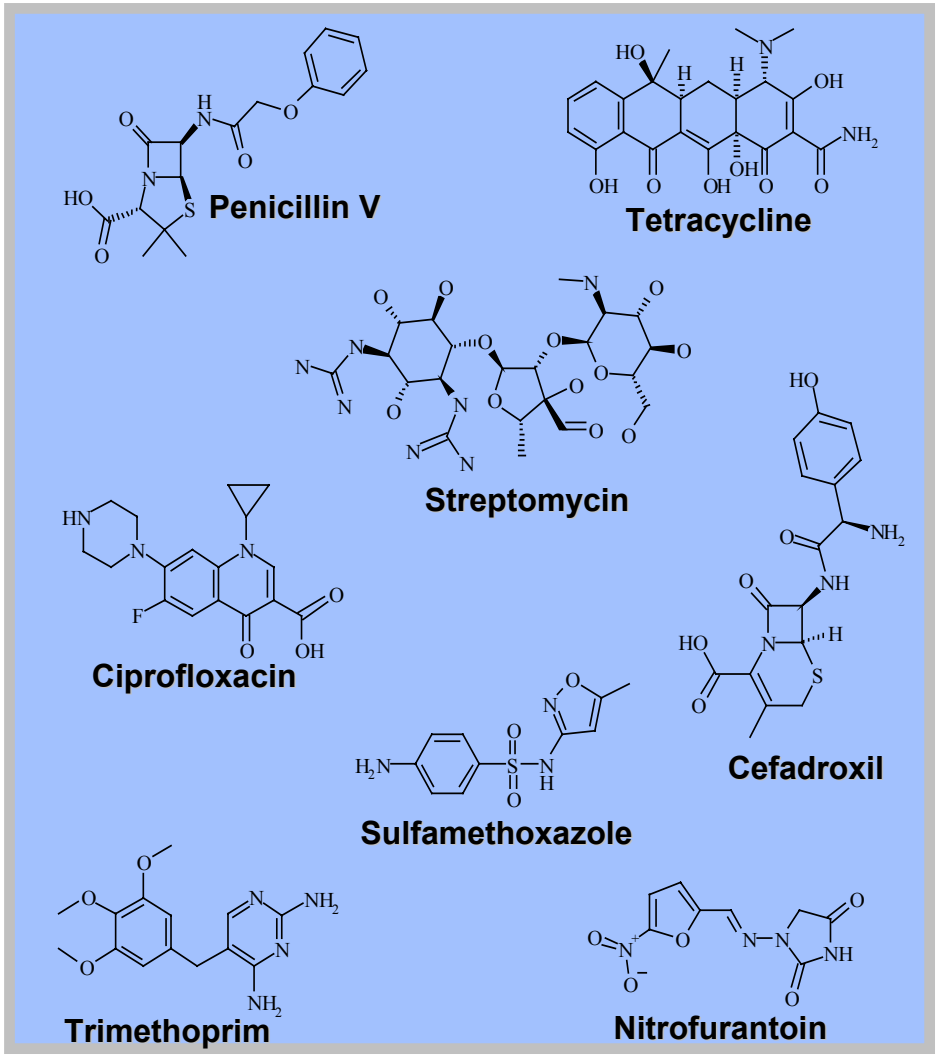
Molecular hashkeys measure surface properties of molecules by seeing "who they look like"



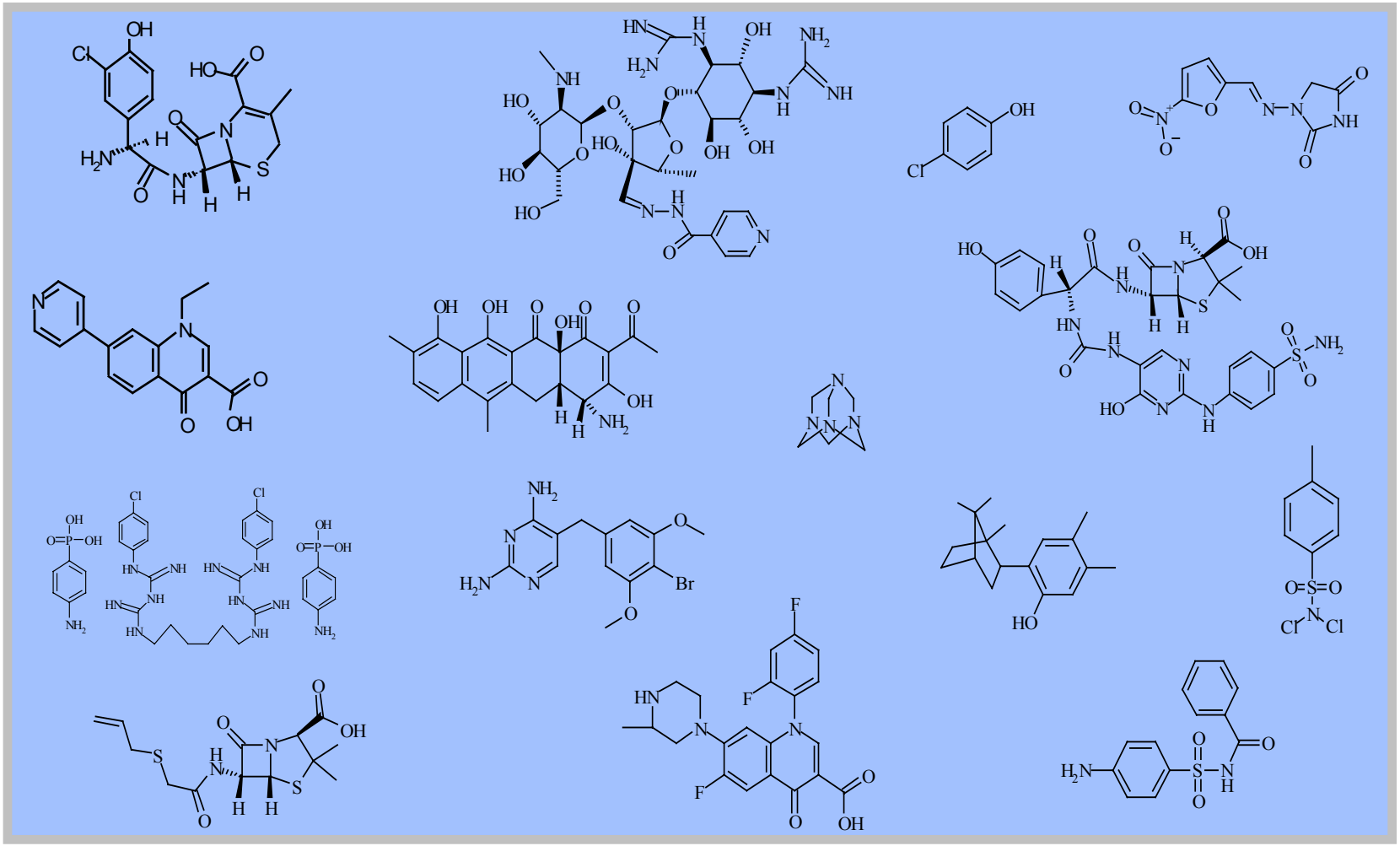


Diversity Analysis of Antibacterials

- **450 antibacterials in the CMC**
- **Small number of protein targets and chemical classes**
  - **Cephalosporins: 74**
  - **"Mycins": 74**
  - **Penicillins: 62**
  - **Sulfa drugs: 49**
  - **Quinolones: 27**
  - **Nitrofurantoin + analogs: 23**
  - **Tetracyclines: 21**
  - **Miscellaneous (dermatologicals etc...)**
- **We can automatically select a small diverse subset that hits all classes**



Diverse set of 15 covers all classes

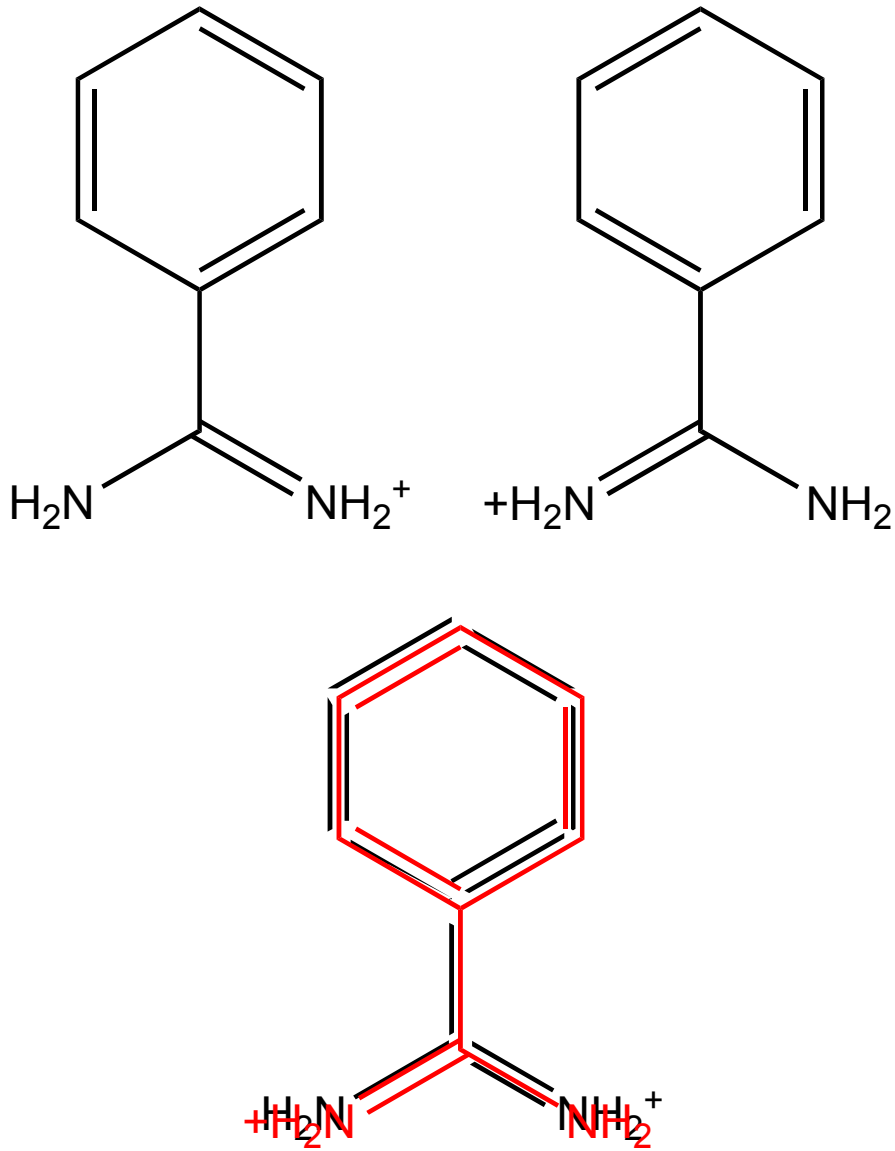


Chosen by maximizing diversity of 450 molecular hashkeys

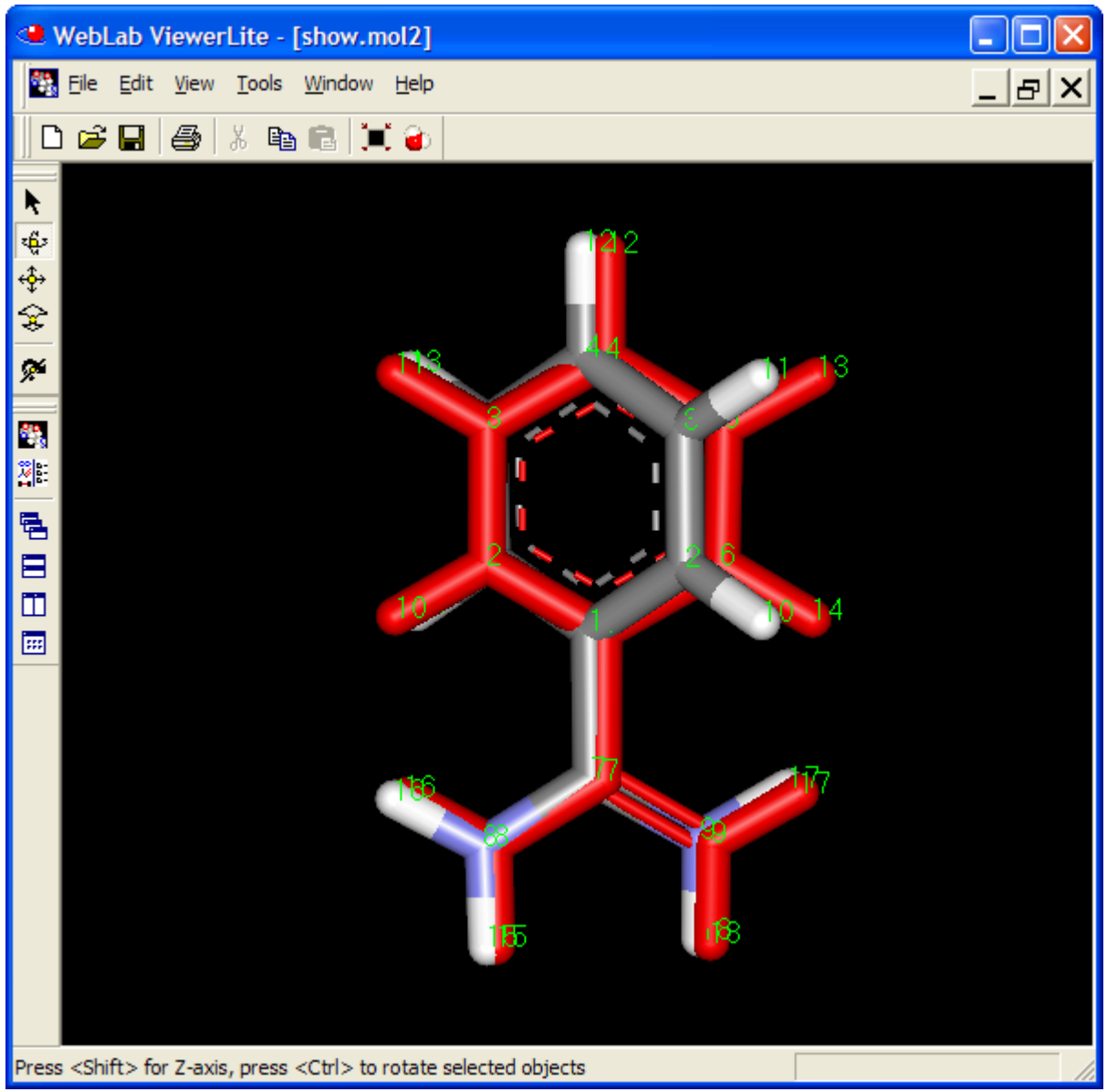
Docking accuracy

- We have a ligand of a protein and dock it into the protein
- We have determined the crystal structure of the protein ligand complex
- We can define the accuracy of the docking as the rmsd of the heavy atoms (non-hydrogens)
- Rmsd = sqrt(sum of squared deviations)

A molecule with symmetries may be correctly docked but have high nominal rmsd



rmsd = 1.5 but should be 0.5



Sybyl mol2 file format

```
@<TRIPOS>MOLECULE
ran-00-ligand
 18 18 0 0 0
SMALL
NO_CHARGES


@<TRIPOS>ATOM
      1 C          -1.221    -4.911    -4.953  C
      2 C          -1.784    -4.887    -6.202  C
      3 C          -2.990    -5.559    -6.437  C
      4 C          -3.629    -6.253    -5.397  C
      5 C          -3.047    -6.261    -4.127  C
      6 C          -1.846    -5.587    -3.920  C
      7 C           0.084    -4.195    -4.703  C
      8 N           0.366    -3.685    -3.541  N
      9 N           1.022    -4.226    -5.603  N
     10 H          -1.297    -4.349    -7.006  H
     11 H          -3.432    -5.543    -7.426  H
     12 H          -4.561    -6.776    -5.577  H
     13 H          -3.526    -6.788    -3.309  H
     14 H          -1.394    -5.591    -2.935  H
     15 H           1.263    -3.201    -3.395  H
     16 H          -0.309    -3.764    -2.767  H
     17 H           0.831    -4.624    -6.533  H
     18 H           1.957    -3.852    -5.385  H
```

```
@<TRIPOS>BOND
     1    1    7 1
     2    1    6 ar
     3    1    2 ar
     4    2    3 ar
     5    3    4 ar
     6    4    5 ar
     7    5    6 ar
     8    7    9 2
     9    7    8 1
    10    2   10 1
    11    3   11 1
    12    4   12 1
    13    5   13 1
    14    6   14 1
    15    8   15 1
    16    8   16 1
    17    9   17 1
    18    9   18 1
```

Homework 2: Due April 13th

- Write a program that will compute the minimum rmsd between two molecules over all isomorphic projections
- Input: a list of pathnames to pairs of molecule files
- Output
  - Actual rmsd (atom number equivalence)
  - Min rmsd under isomorphism
  - Correspondence of atoms that gave rise to the min rmsd
- You should not check bond order equivalence, since it will cause trouble
- Instead, check atom equivalence
  - Atoms A and B are the same element
  - They have the same number of substituents
  - Their substituents are the same elements
- Only worry about the following elements: C N O S P F Cl Br I

What to turn in

- A listing of your program
- The output of your program on Pathlist (sensibly formatted)
- Brief discussion of the complexity of your algorithm
- Email 1 file to ajain@cc.ucsf.edu