Lecture 13: Graph Algorithms

Study Chapter 8.1 – 8.8

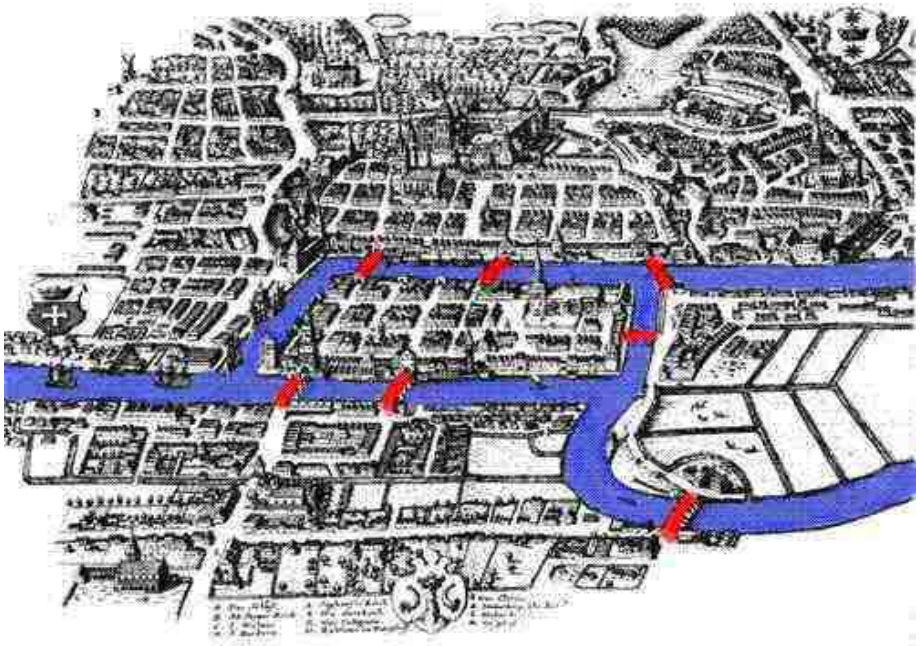
Abbreviated class meeting Thursday
(and Homework #2 is due)

MidTerm a week from Thursday, October 13

It will cover through Lecture 12, Chapter 7

The Bridge Obsession Problem

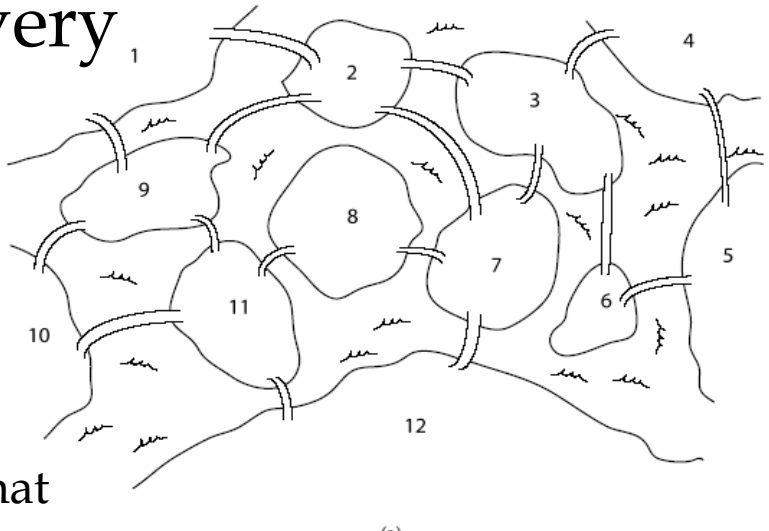
Find a tour crossing every bridge just once
Leonhard Euler, 1735



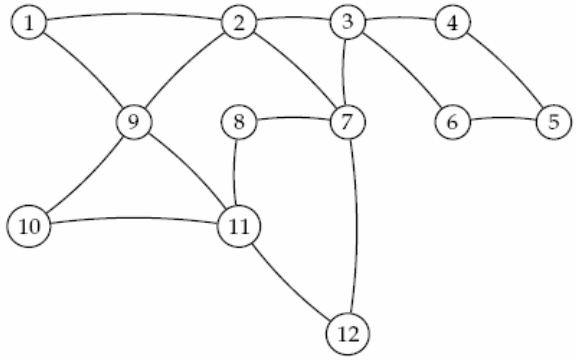
Bridges of Königsberg

Eulerian Cycle Problem

- Find a cycle that visits every *edge* exactly once
- Linear time
  - Starting at any vertex v, and follow a trail of edges until returning to v.
  - As long as there exists a vertex v that belongs to the current tour, but has adjacent edges not part of the tour, start a new trail from v, following unused edges until returning to v, and join the tour formed in this way to the previous tour.
  - Special case vertices with odd degree



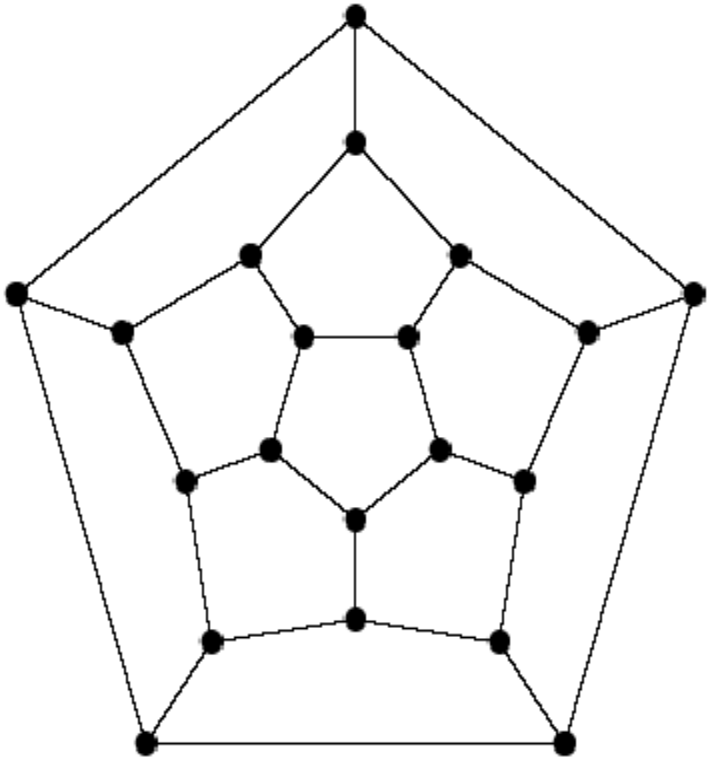
(a)



More complicated Königsberg

Hamiltonian Cycle Problem

- Find a cycle that visits every ***vertex*** exactly once
- Deceptively similar to the Eulerian path
- NP-complete

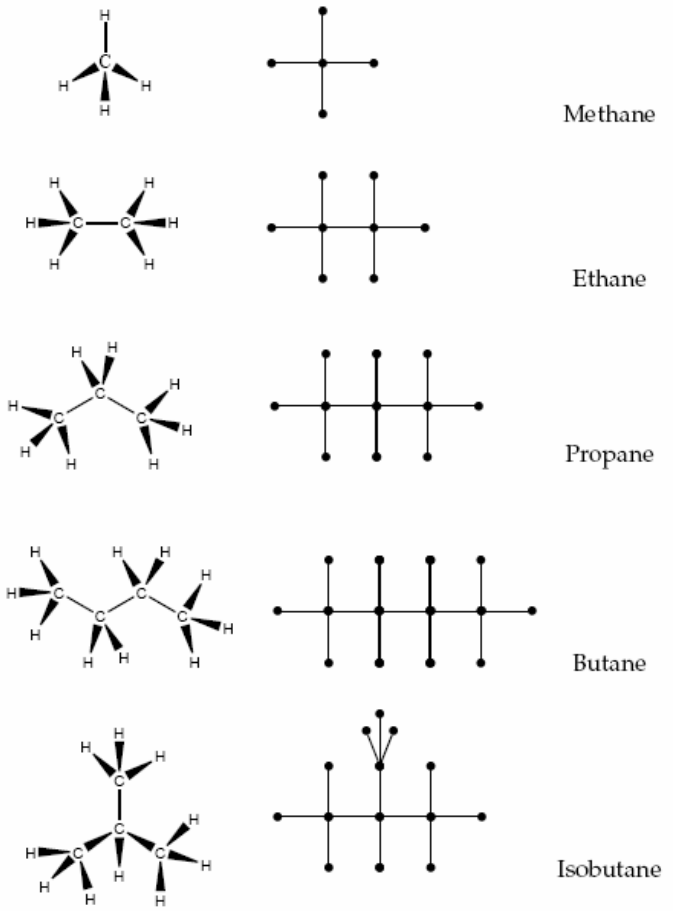


Game invented by Sir William Hamilton in 1857

Mapping Problems to Graphs

- *Arthur Cayley* studied chemical structures of hydrocarbons in the mid-1800s

- He used **trees** (acyclic connected graphs) to enumerate structural isomers



Beginning of Graph Theory in Biology

Benzer's work

- Developed deletion mapping
- "Proved" linearity of the gene
- Demonstrated internal structure of the gene

Seymour Benzer, 1950s

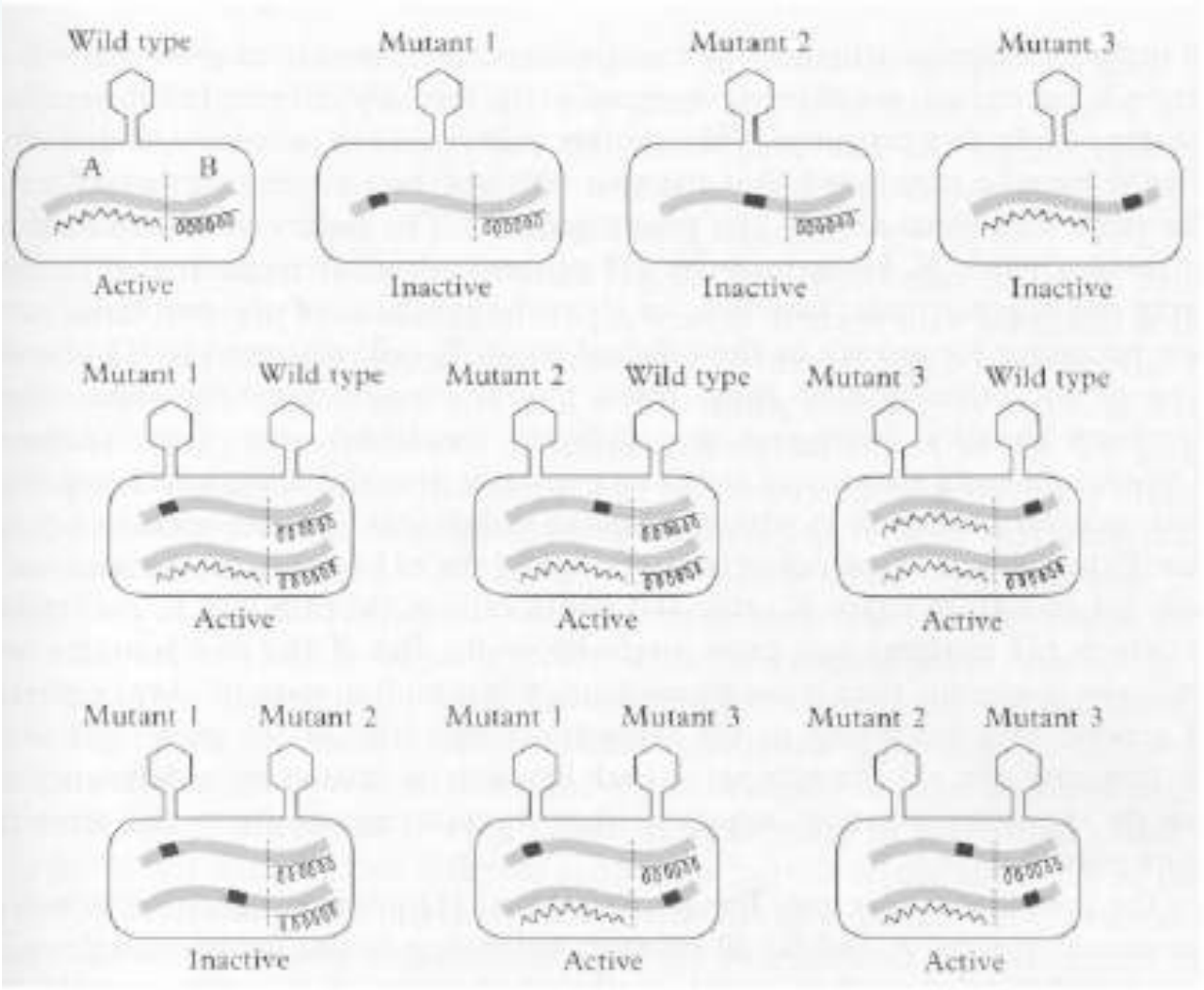
Viruses Attack Bacteria

- Normally bacteriophage T4 kills bacteria
- However if T4 is mutated (e.g., an important gene is deleted) it gets disable and looses an ability to kill bacteria
- Suppose the bacteria is infected with two different mutants each of which is disabled – would the bacteria still survive?
- Amazingly, a pair of disabled viruses can kill a bacteria even if each of them is disabled.
- How can it be explained?

Benzer's Experiment

- Idea: infect bacteria with pairs of mutant T4 bacteriophage (virus)
- Each T4 mutant has an unknown interval deleted from its genome
- If the two intervals overlap: T4 pair is missing part of its genome and is disabled – bacteria survive
- If the two intervals do not overlap: T4 pair has its entire genome and is enabled – bacteria die

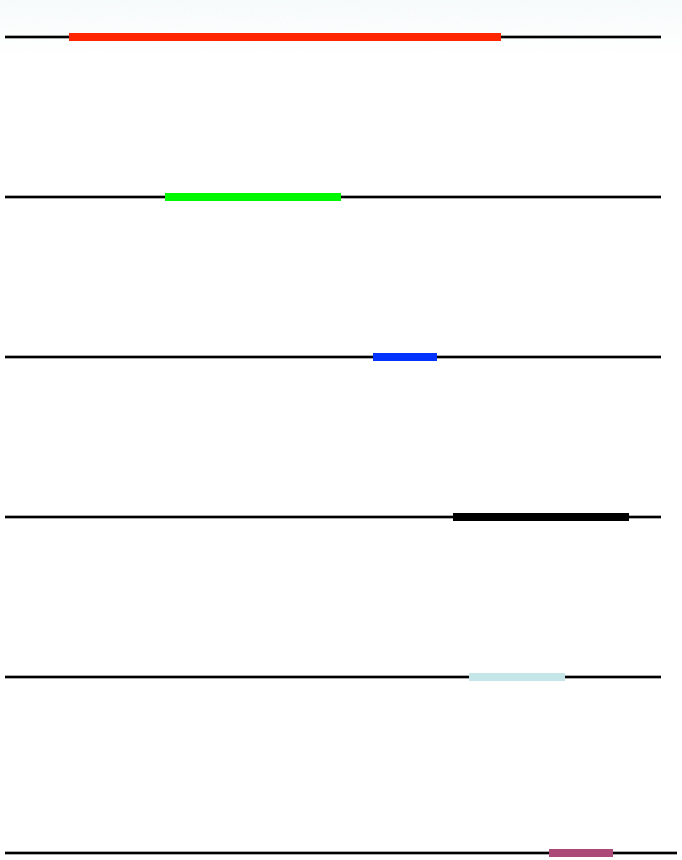
Complementation between pairs of mutant T4 bacteriophages

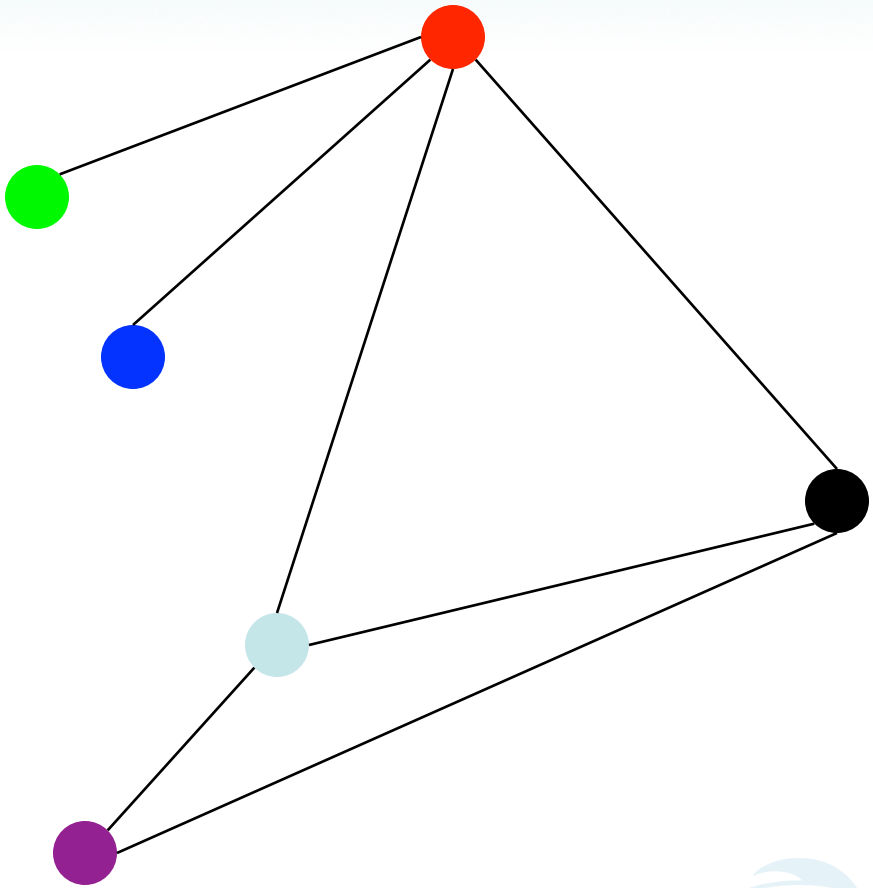


Benzer's Experiment and Graphs

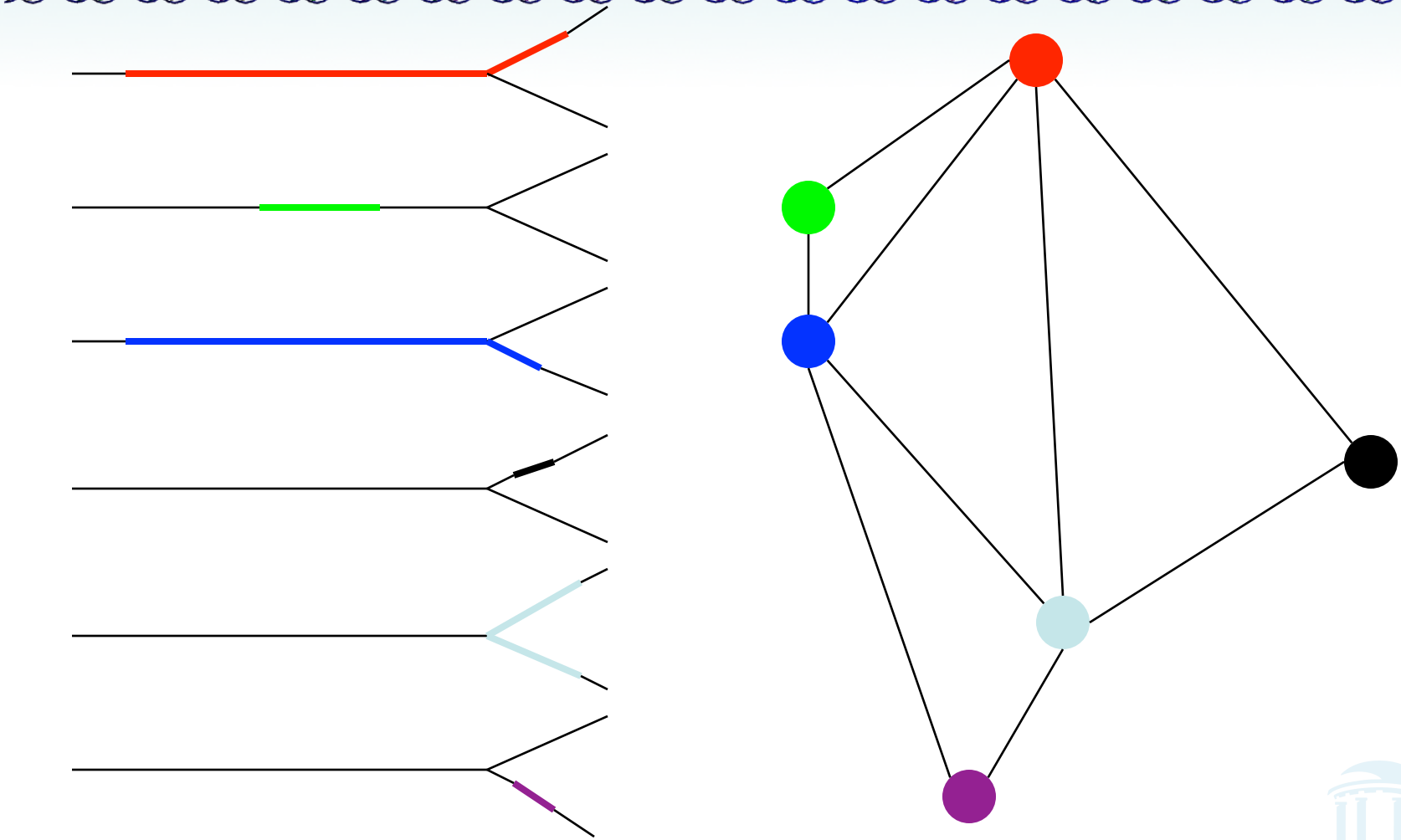
- Construct an **interval graph**: each T4 mutant is a vertex, place an edge between mutant pairs where bacteria survived (i.e., the deleted intervals in the pair of mutants overlap)
- Interval graph structure reveals whether DNA is linear or branched DNA

Interval Graph: Linear Genes

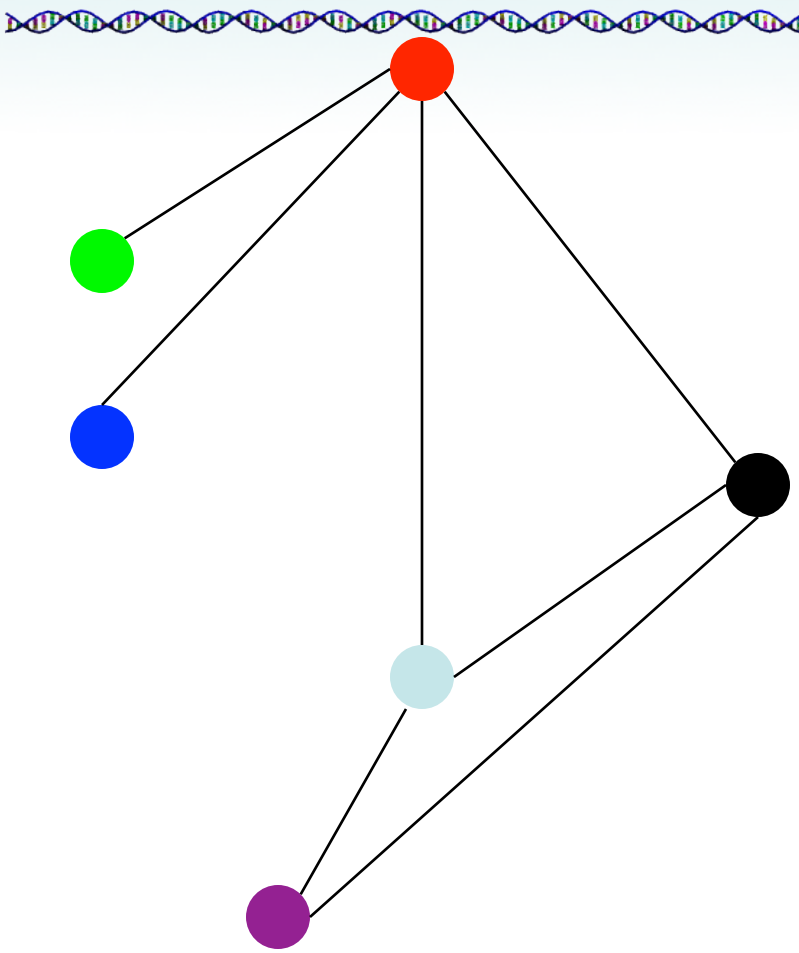




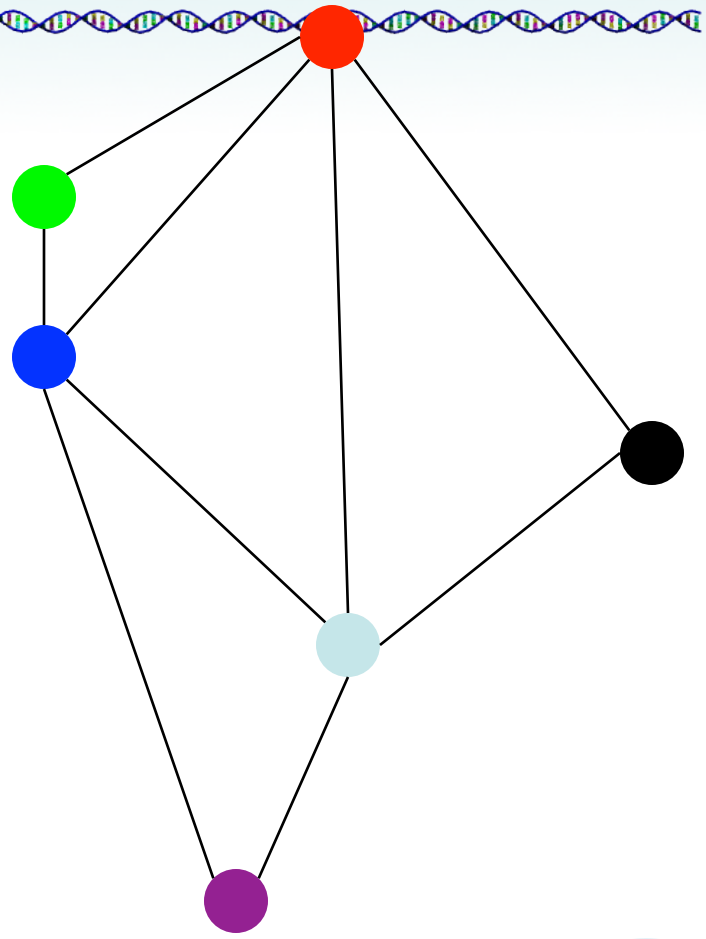
Interval Graph: Branched Genes



Interval Graph: Comparison



Linear genome



Branched genome

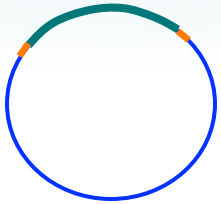
DNA Sequencing: History

Sanger method (1977):
labeled ddNTPs terminate DNA copying at random points.

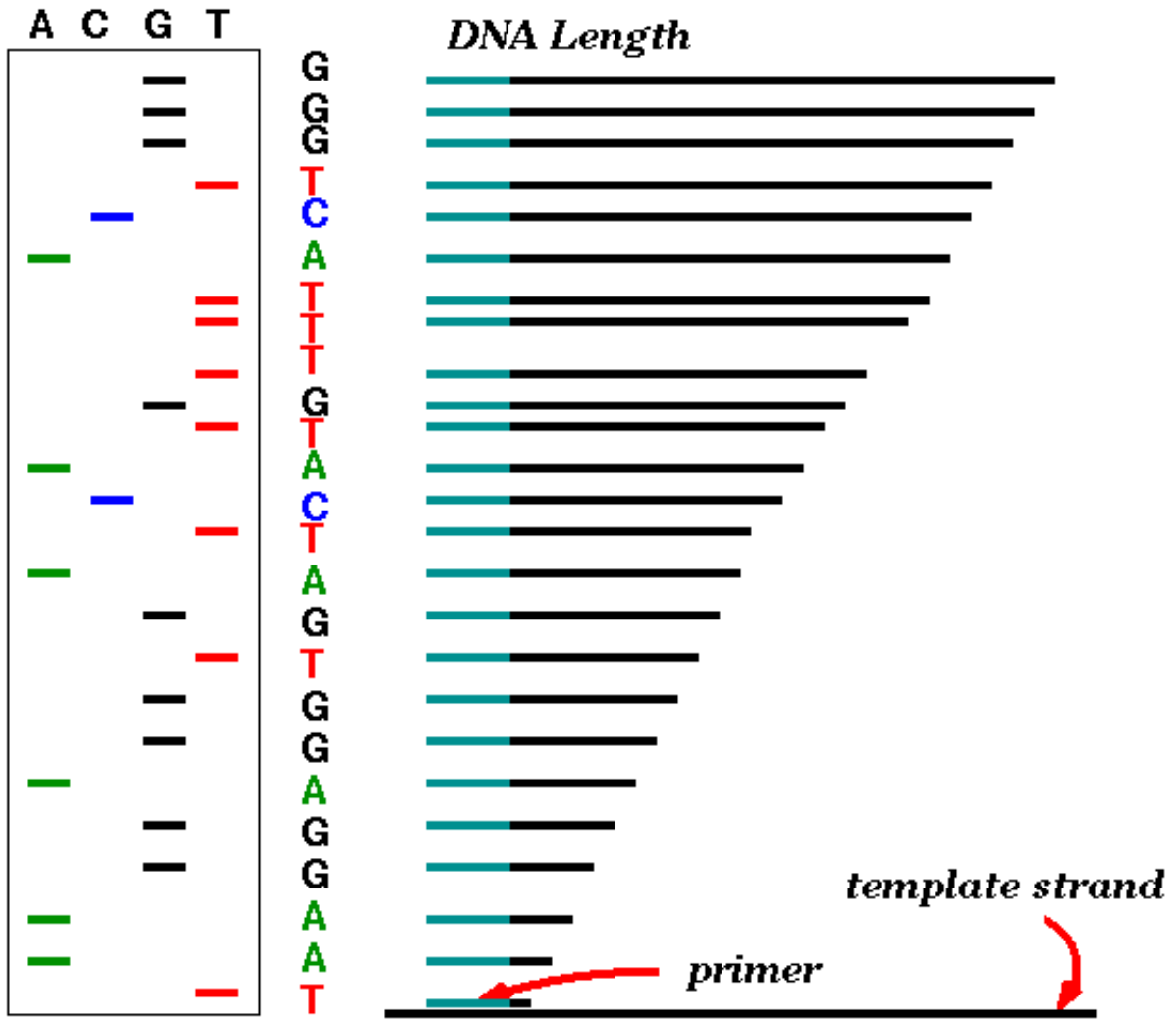
Gilbert method (1977):
chemical method to cleave DNA at specific points (G, G+A, T+C, C).

Both methods generate labeled fragments of varying lengths that are further electrophoresed.

Sanger Method: Generating Read

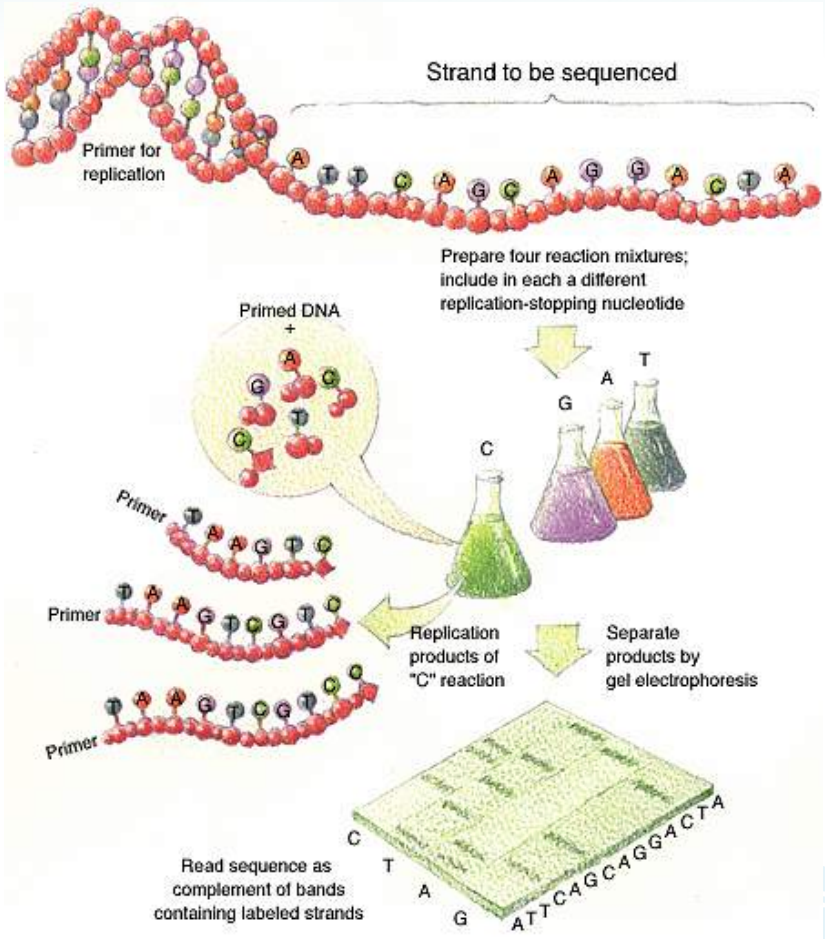


1. Start at primer (restriction site)
2. Grow DNA chain
3. Include ddNTPs
4. Stops reaction at all possible points
5. Separate products by length, using gel electrophoresis



DNA Sequencing

- Shear DNA into millions of small fragments
- Read 500 – 700 nucleotides at a time from the small fragments (Sanger method)



Fragment Assembly

- **Computational Challenge:** assemble individual short fragments (reads) into a single genomic sequence ("superstring")

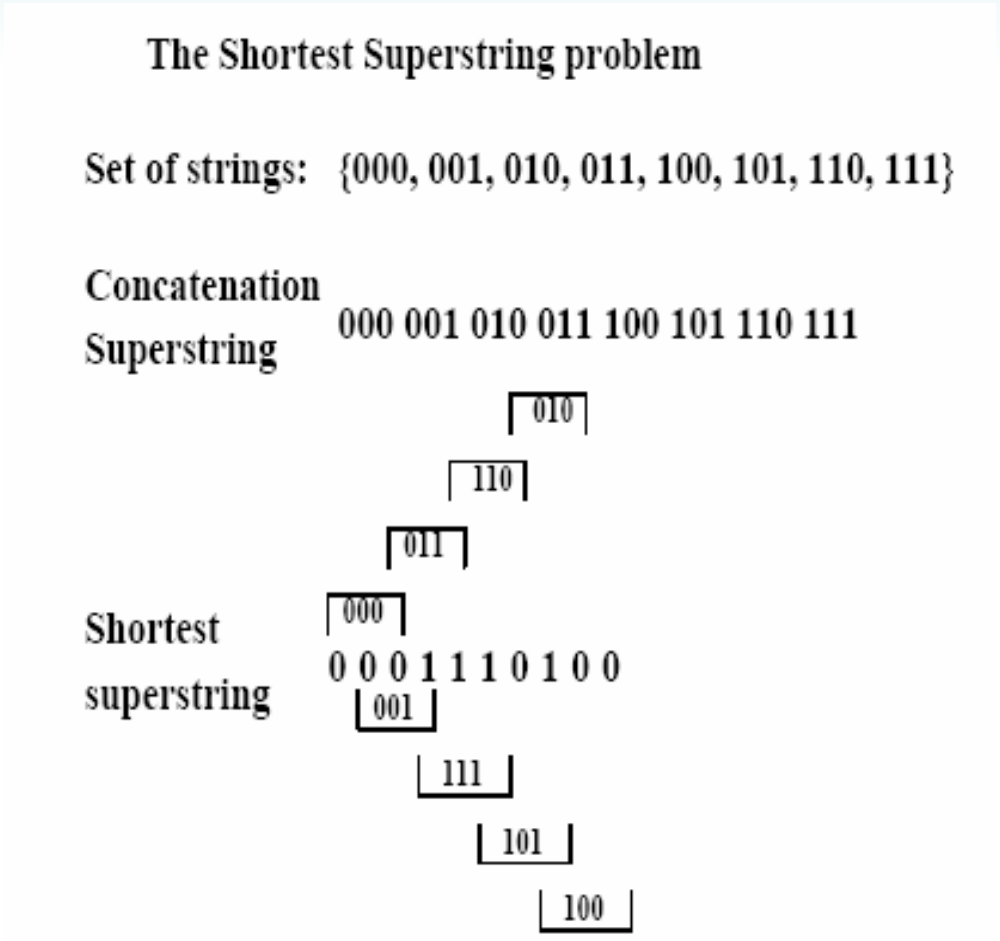
- Until late 1990s the shotgun fragment assembly of human genome was viewed as intractable problem

Shortest Superstring Problem

- Problem: Given a set of strings, find a shortest string that contains all of them
- Input: Strings $s_1, s_2, \ldots, s_n$
- Output: A string s that contains all strings $s_1, s_2, \ldots, s_n$ as substrings, such that the length of s is minimized

- **Complexity:** NP – complete
- **Note:** this formulation does not take into account sequencing errors

Shortest Superstring Problem: Example



Reducing SSP to TSP

- Define *overlap* (s_i, s_j) as the length of the longest prefix of s_j that matches a suffix of s_i.

  aaaggcatcaaatctaaaggcatcaaa

  aaaggcatcaaatctaaaggcatcaaa

What is** overlap (s_i, s_j) **for these strings?

Reducing SSP to TSP

- Define *overlap* (s_i, s_j) as the length of the longest prefix of s_j that matches a suffix of s_i.

  aaaggcatcaaatctaaaggcatcaaa

  aaaggcatcaaatctaaaggcatcaaa

  overlap=12

Reducing SSP to TSP

- Define *overlap* (s_i, s_j) as the length of the longest prefix of s_j that matches a suffix of s_i.

  aaaggcatcaaatctaaaggcatcaaa

  aaaggcatcaaatctaaaggcatcaaa

- Construct a graph with n vertices representing the n strings s_1, s_2, …., s_n.
- Insert edges of length *overlap* (s_i, s_j) between vertices s_i and s_j.
- Find the shortest path which visits every vertex exactly once. This is the **Traveling Salesman Problem** (TSP), which is also NP – complete.

SSP to TSP: An Example

S = { ATC, CCA, CAG, TCC, AGT }

SSP

AGT

CCA

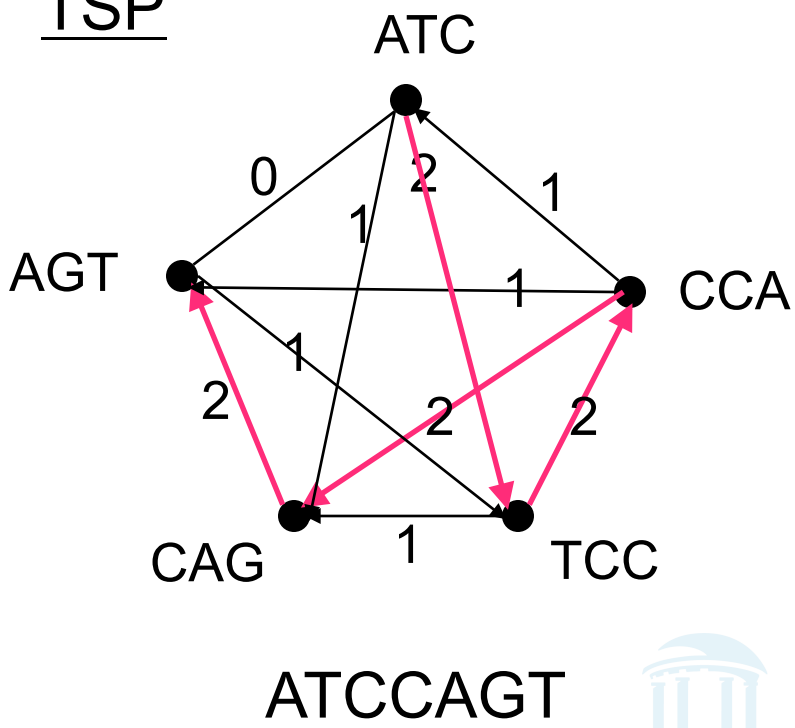
ATC

ATCCAGT

TCC

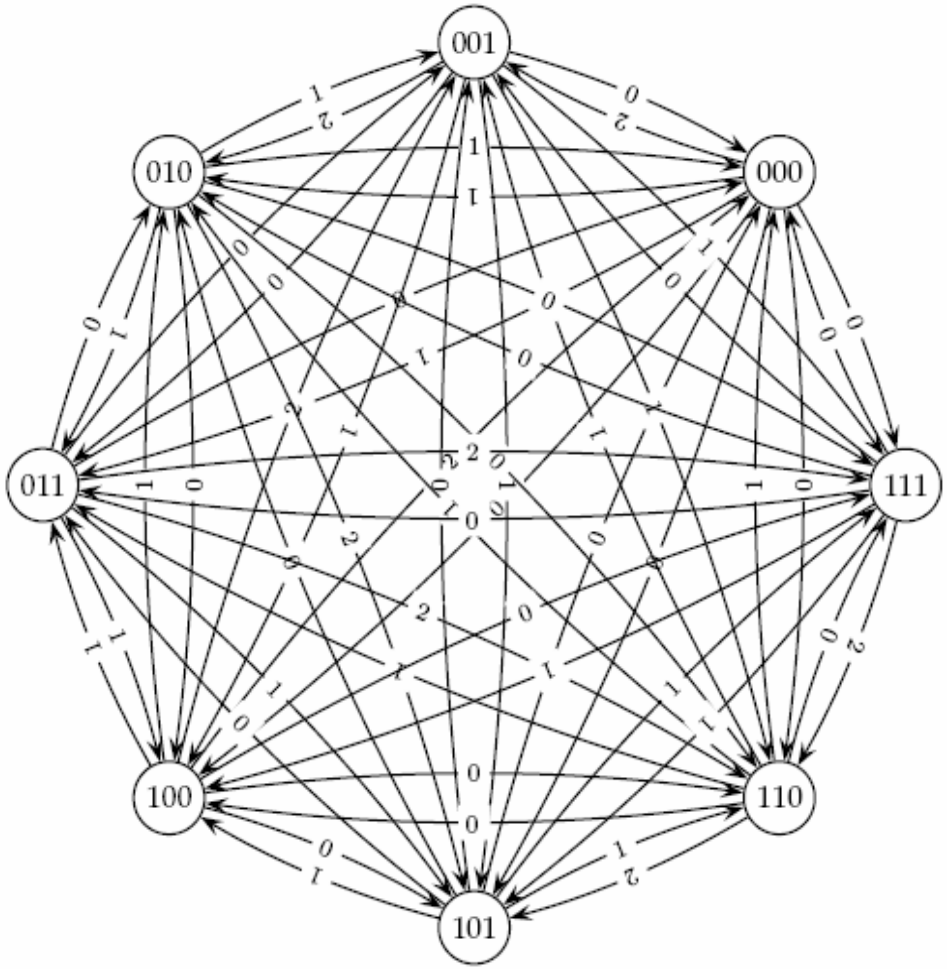
CAG

TSP



ATCCAGT

Reducing SSP to TSP (cont'd)

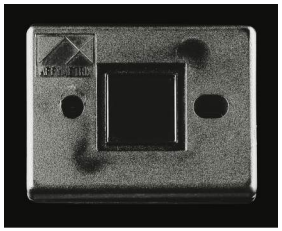


Sequencing by Hybridization (SBH): History

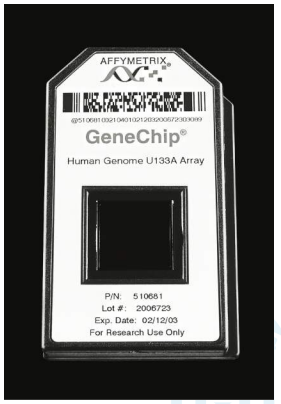
- **1988:** SBH suggested as an alternative sequencing method. Nobody believed it will ever work
- **1991:** Light directed polymer synthesis developed by Steve Fodor and colleagues.
- **1994:** Affymetrix develops first 64-kb DNA microarray

*First microarray prototype **(1989)***

*First commercial DNA microarray prototype w/16,000 features **(1994)***



*500,000 features per chip **(2002)***



How SBH Works

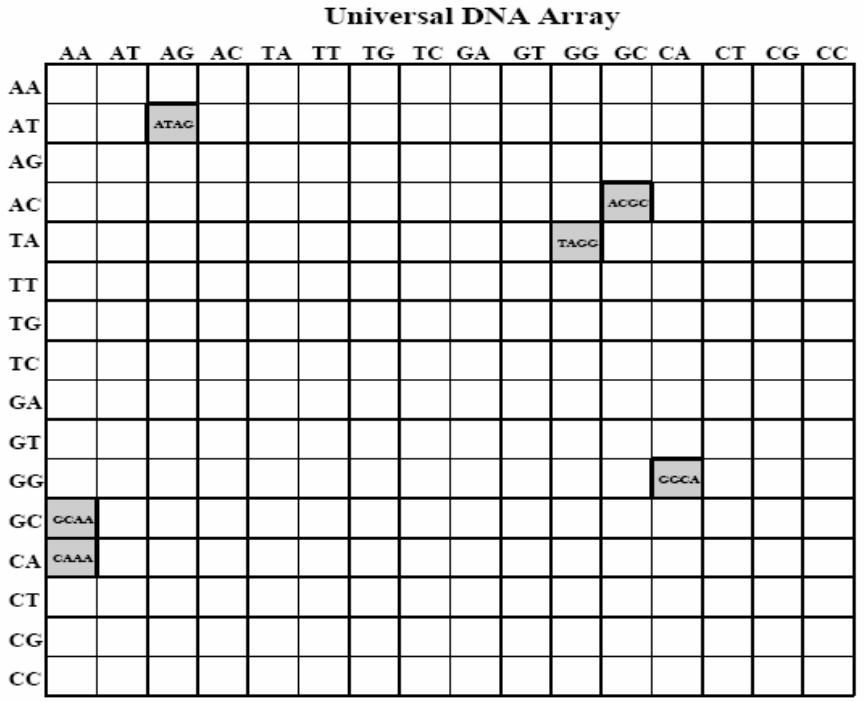
- Attach all possible DNA probes of length *l* to a flat surface, each probe at a distinct and known location. This set of probes is called the DNA array.
- Apply a solution containing fluorescently labeled DNA fragment to the array.
- The DNA fragment hybridizes with those probes that are complementary to substrings of length *l* of the fragment.

How SBH Works (cont'd)

- Using a spectroscopic detector, determine which probes hybridize to the DNA fragment to obtain the *l*–mer composition of the target DNA fragment.

- Apply the combinatorial algorithm (below) to reconstruct the sequence of the target DNA fragment from the *l*–mer composition.

Hybridization on DNA Array



DNA target TATCCGTTT (complement of ATAGGCAAA)
hybridizes to the array of all 4-mers:

```
A T A G G C A A A
A T A G
  T A G G
    A G G C
      G G C A
        G C A A
          C A A A
```

l-mer composition

- ***Spectrum (s, l)*** - *unordered* multiset of all possible *(n – l + 1) l*-mers in a string *s* of length *n*
- The order of individual elements in *Spectrum (s, l)* does not matter
- For *s* = TATGGTGC all of the following are equivalent representations of *Spectrum (s, 3):*

  {TAT, ATG, TGG, GGT, GTG, TGC}

  {ATG, GGT, GTG, TAT, TGC, TGG}

  {TGG, TGC, TAT, GTG, GGT, ATG}

l-mer composition

- ***Spectrum (s, l)*** - *unordered* multiset of all possible *(n – l + 1) l*-mers in a string *s* of length *n*
- The order of individual elements in *Spectrum (s, l)* does not matter
- For *s* = TATGGTGC all of the following are equivalent representations of *Spectrum (s, 3):*

  {TAT, ATG, TGG, GGT, GTG, TGC}

  {ATG, GGT, GTG, TAT, TGC, TGG}

  {TGG, TGC, TAT, GTG, GGT, ATG}

- We usually choose the lexicographically maximal representation as the canonical one.

Different sequences – the same spectrum

- Different sequences may have the same spectrum:

  Spectrum(GTATCT,2)=

  Spectrum(GTCTAT,2)=

  {AT, CT, GT, TA, TC}

The SBH Problem

- Goal: Reconstruct a string from its *l*-mer composition

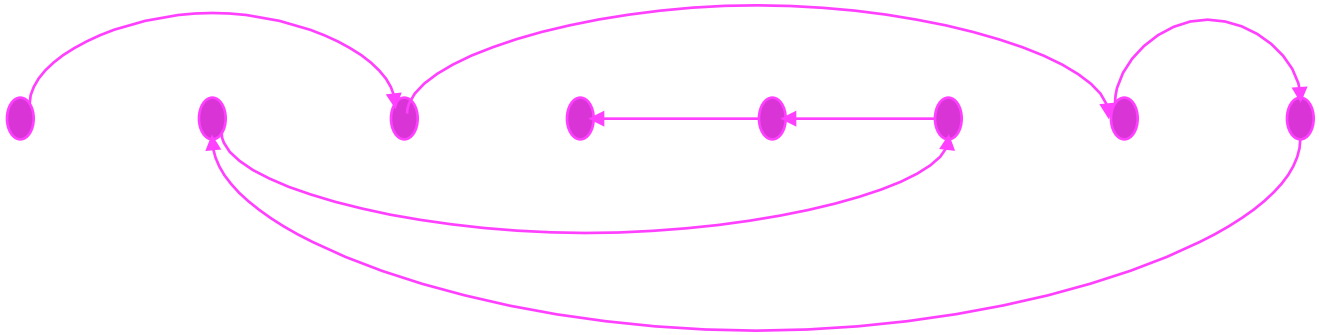
- Input: A set *S*, representing all *l*-mers from an (unknown) string *s*

- Output: String *s* such that *Spectrum (s,l)* = *S*

SBH: Hamiltonian Path Approach

S = { ATG AGG TGC TCC GTC GGT GCA CAG }

ATG AGG TGC TCC GTC GGT GCA CAG



ATGCAGGTCC

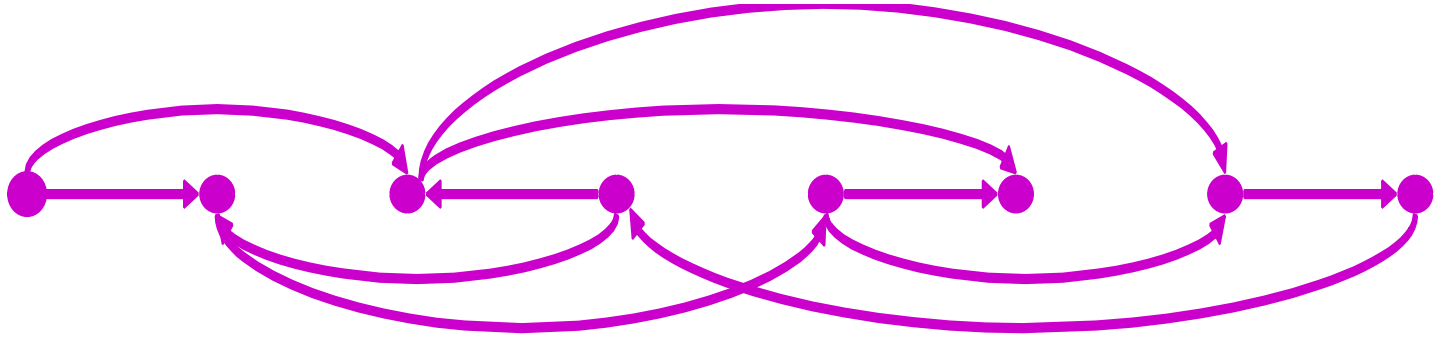
Path visited every VERTEX once

SBH: Hamiltonian Path Approach

A more complicated graph:

S = { ATG TGG TGC GTG GGC GCA GCG CGT }

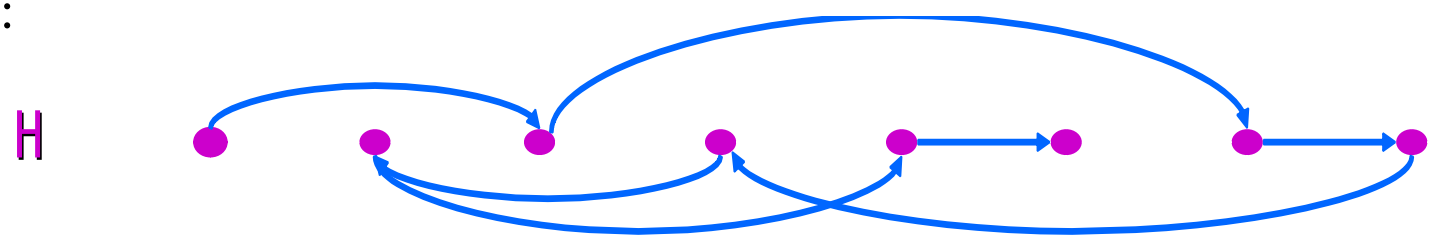
H



SBH: Hamiltonian Path Approach

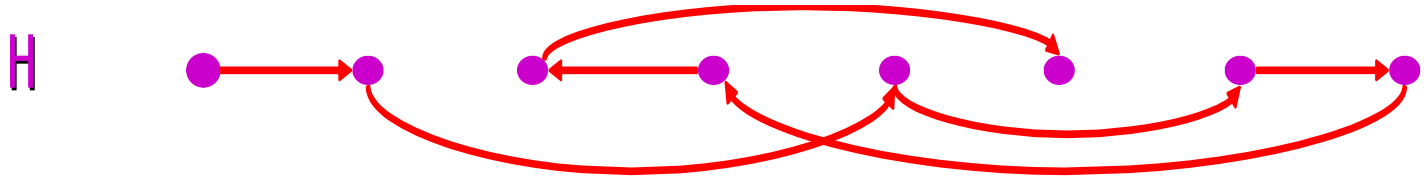
S = { ATG TGG TGC GTG GGC GCA GCG CGT }

Path 1:



ATGCGTGGCA

Path 2:



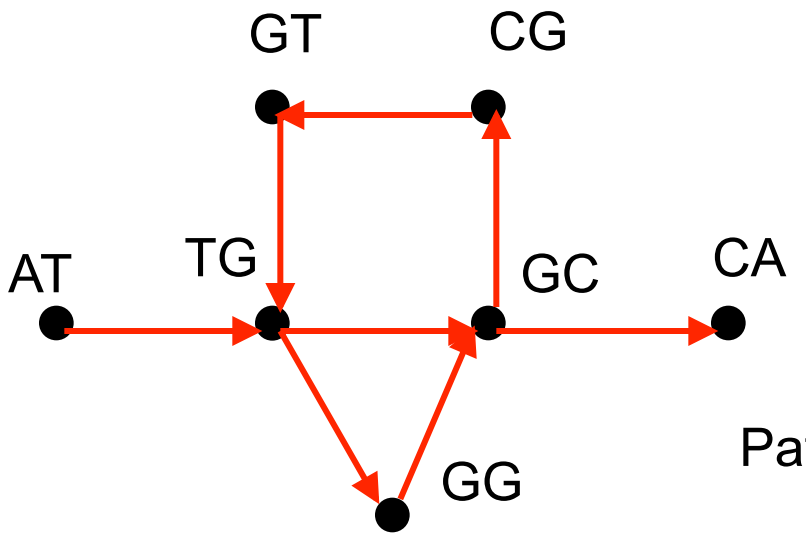
ATGGCGTGCA

SBH: Eulerian Path Approach

S = { ATG, TGG, TGC, GTG, GGC, GCA, GCG, CGT }

Vertices correspond to (l – 1) – mers : { AT, TG, GC, GG, GT, CA, CG }

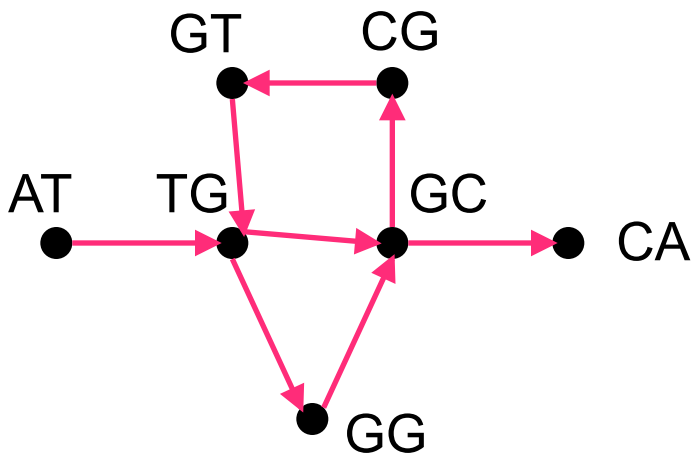
Edges correspond to l – mers from S



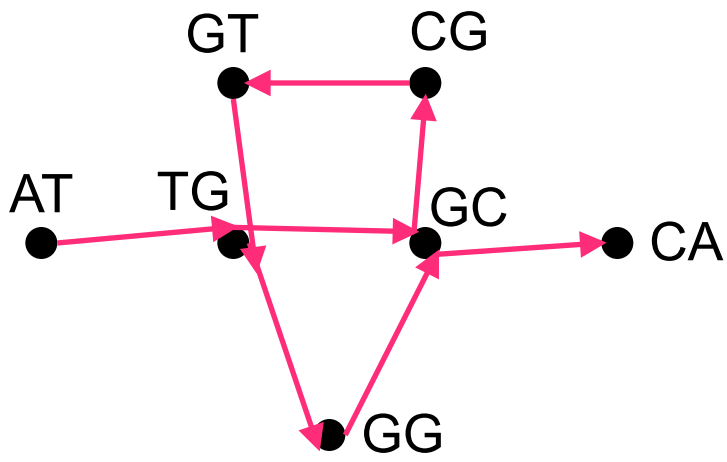
Path visited every EDGE once

SBH: Eulerian Path Approach

S = { AT, TG, GC, GG, GT, CA, CG } corresponds to two different paths:



ATGGCGTGCA



ATGCGTGGCA

Euler Theorem

- A graph is balanced if for every vertex the number of incoming edges equals to the number of outgoing edges:

$$in(v)=out(v)$$

- **Theorem**: *A connected graph is Eulerian if and only if each of its vertices is balanced.*

Euler Theorem: Proof

- Eulerian → balanced

  for every edge entering v (incoming edge) there exists an edge leaving v (outgoing edge). Therefore

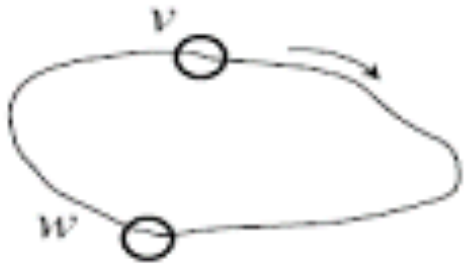
  $$in(v)=out(v)$$

- Balanced → Eulerian

  ???

Algorithm for Constructing an Eulerian Cycle

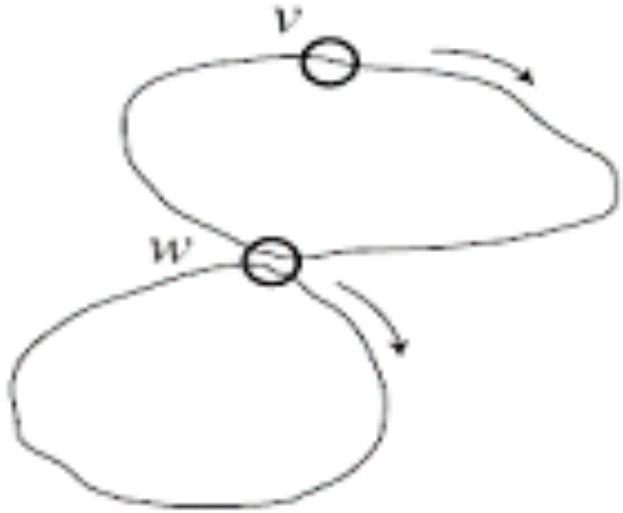
a. Start with an arbitrary vertex v and form an arbitrary cycle with unused edges until a dead end is reached. Since the graph is Eulerian this dead end is necessarily the starting point, i.e., vertex v.



(a)

Algorithm for Constructing an Eulerian Cycle (cont'd)

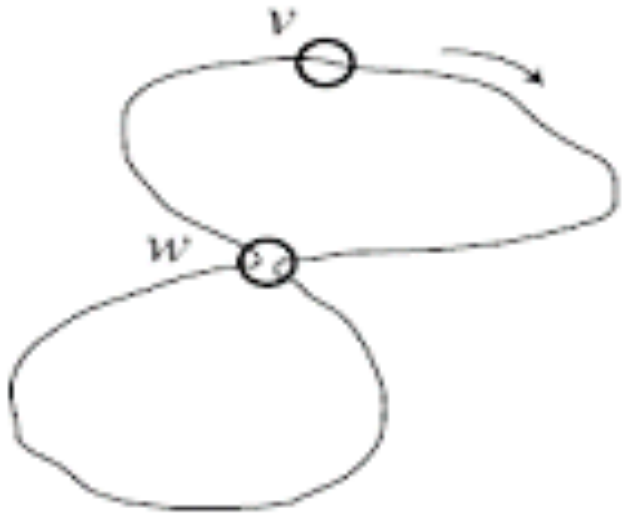
b. If cycle from (a) above is not an Eulerian cycle, it must contain a vertex w, which has untraversed edges. Perform step (a) again, using vertex w as the starting point. Once again, we will end up in the starting vertex w.



(b)

Algorithm for Constructing an Eulerian Cycle (cont'd)

c. Combine the cycles from (a) and (b) into a single cycle and iterate step (b).



(c)

Running time: linear to the number of edges

Euler Theorem: Extension

- **Theorem**: *A connected graph has an Eulerian path if and only if it contains at most two semi-balanced vertices and all other vertices are balanced.*
  - Semi-balanced vertex: *in*(v) and *out*(v) differ by 1

Some Difficulties with SBH

- **Fidelity of Hybridization:** difficult to detect differences between probes hybridized with perfect matches and 1 or 2 mismatches
- **Array Size:** Effect of low fidelity can be decreased with longer *l*-mers, but array size increases exponentially in *l*. Array size is limited with current technology.
- **Practicality:** SBH is still impractical. As DNA microarray technology improves, SBH may become practical in the future
- **Practicality again**: Although SBH is still impractical, it spearheaded expression analysis and SNP analysis techniques