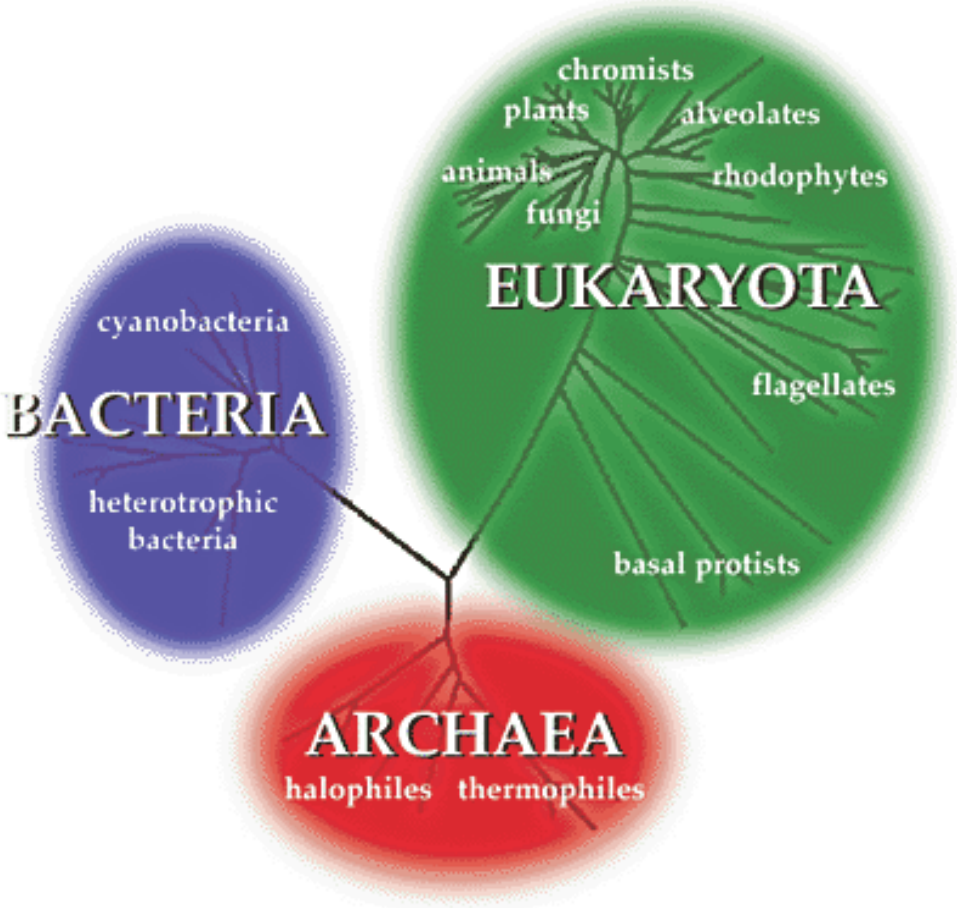
10.555 Bioinformatics

Principles, Methods, Applications


chromists
plants
alveolates
animals
rhodophytes
fungi
EUKARYOTA
cyanobacteria
BACTERIA
flagellates
heterotrophic
bacteria
basal protists
ARCHAEA
halophiles
thermophiles

GenBank Statistics

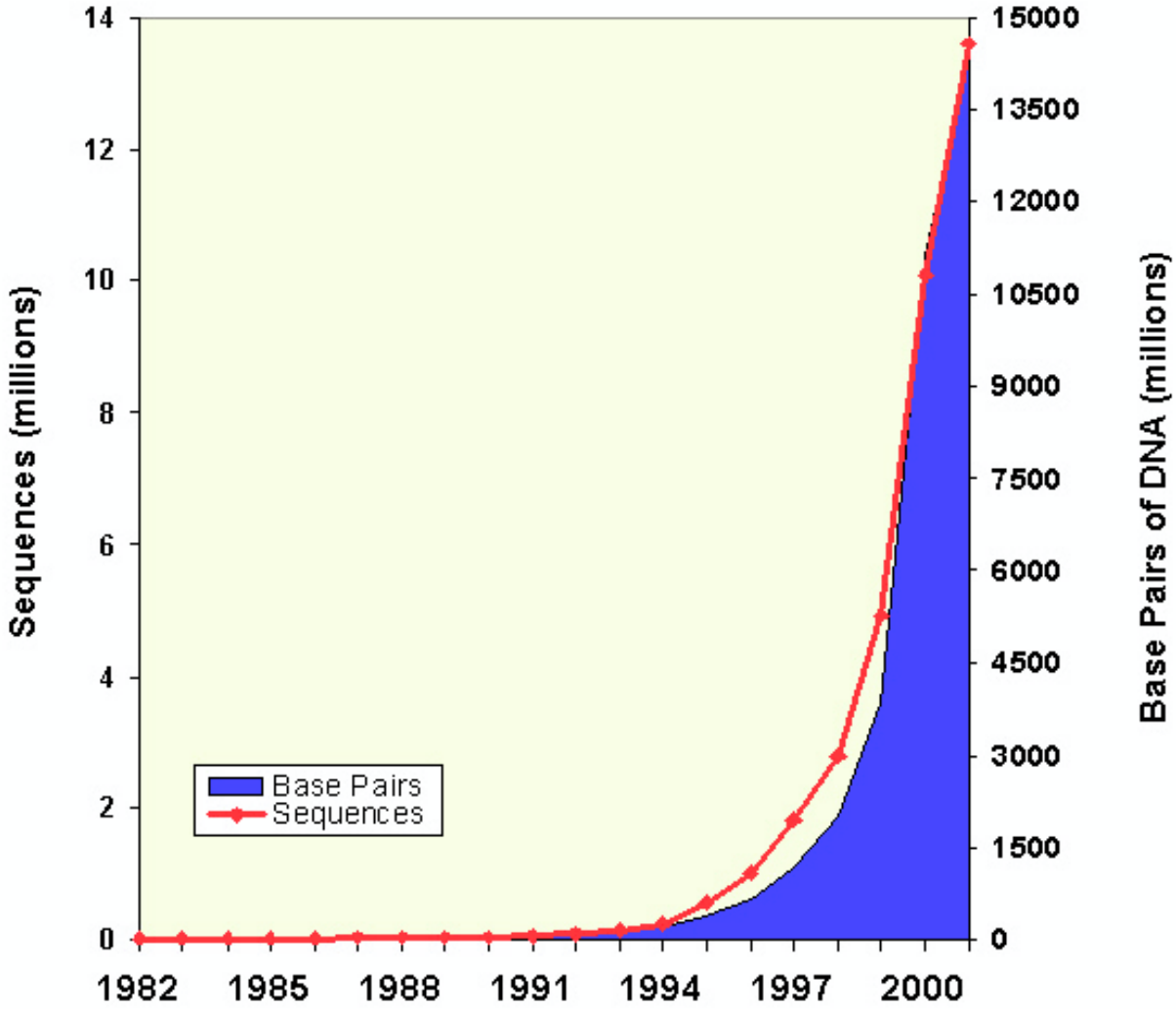


Figure from:
http://www.ncbi.nlm.nih.gov/Genbank/genbankstats.html

Glossaries

Glossary of Genetics Terms:
http://www.nhgri.nih.gov/DIR/VIP/Glossary/pub_glossary.cgi

Glossary of Computer Science Terms:
http://foldoc.doc.ic.ac.uk/foldoc/index.html

Another Glossary of Genetics Terms:
http://www.bis.med.jhmi.edu/Dan/DOE/prim6.html

A Hypermedia Glossary of Genetics Terms:
http://www.weihenstephan.de/~schlind/genglos.html

An Interactive Glossary of Latin Terms:
http://lysy2.archives.nd.edu/cgi-bin/words.exe

Multilingual Glossary of Technical and Popular Medical Terms in 9 European Languages
http://allserv.rug.ac.be/~rvdstich/eugloss/welcome.html

Database Link

GenBank / GenPept http://www.ncbi.nlm.nih.gov/

dna, protein, est, individual genomes, gene expression data etc. from all over the world.11,101,066,288 bases in 10,106,023 sequence records as of February 2001

PIR http://www-nbrf.georgetown.edu/pir/

Collaboration btw the Protein Information Resource (PIR), the Munich Information Center for Protein Sequences (MIPS) and the Japanese International Protein Sequence Database (JIPID). A comprehensive, annotated, and non-redundant protein sequence database in which entries are classified into family groups and alignments of each group are available. Current Release 67.03, February 16, 2001, Contains 210045 Entries.

Swiss-Prot + TrEMBL http://www.expasy.ch/sprot

21-Feb-2001: 93,408 entries / TrEMBL: 376,043 entries

PROSITE http://www.expasy.ch/prosite

1040 documentation entries that describe 1386 different patterns, rules and profiles/matrices

PDB / RCSB http://www.rcsb.org/pdb/

12,514 structures as of June 13, 2000

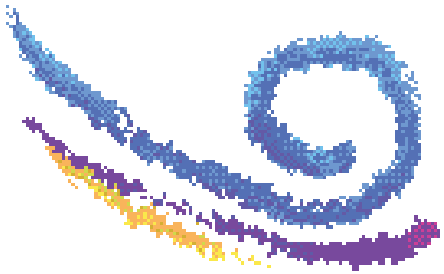
PDB select http://www.sander.embl-heidelberg.de/pdbsel/

GDB http://gdbwww.gdb.org/

the official central repository for genomic mapping data resulting from the Human Genome Initiative

PRODOM http://protein.toulouse.inra.fr/prodom.html

An automatic compilation of homologous domains: 174952 families as of October 1999



Database Links (CONT.)

PROTOMAP http://www.protomap.cs.huji.ac.il/

An exhaustive classification of all proteins in the swissprot database into clusters of related proteins.

COGS http://www.ncbi.nlm.nih.gov/COG/

Clusters of Orthologous Groups of proteins (COGs) were delineated by comparing protein sequences encoded in 34 complete genomes, representing 26 major phylogenetic lineages. Each COG consists of individual proteins or groups of paralogs from at least 3 lineages and thus corresponds to an ancient conserved domain.

GOLD http://wit.integratedgenomics.com/GOLD/

A World Wide Web resource for comprehensive access to information regarding complete and ongoing genome projects around the world.

BLOCKS http://www.blocks.fhcrc.org/

4071 blocks representing 998 groups documented in InterPro 1.0 keyed to SWISS-PROT 38

PFAM http://www.blocks.fhcrc.org/

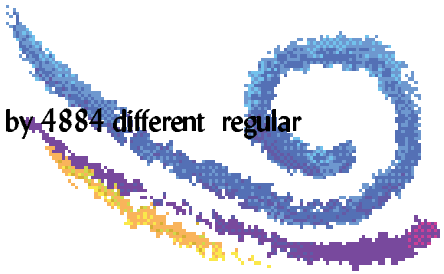
A arge collection of multiple sequence alignments and hidden Markov models covering many common protein domains. Version 5.3 of Pfam (May 2000) contains alignments and models for 2216 protein families, based on the Swissprot 38 and SP-TrEMBL

PRINTS http://www.biochem.ucl.ac.uk/bsm/dbbrowser/PRINTS/PRINTS.html

PRINTS is a compendium of protein fingerprints

INTERPRO http://www.ebi.ac.uk/interpro/

2990 entries, representing 2373 families, 556 domains, 47 repeats and 14 post-translational modification sites encoded by 4884 different regular expressions, profiles, fingerprints and HMMs. (PFAM. PRINTS, PROSITE)



Database Links (CONT.)

IBM Bioinformatics Grp http://www.research.ibm.com/bioinformatics

Web access to engines implementing all of the group's algorithms, plus downloadable Bio-Dictionaries and executable code, description of the group's activities, etc.

EcoCyc http://ecocyc.panbio.com/ecocyc/

Describes the genome and the biochemical machinery of E. coli. EcoCyc is a literature-derived electronic reference source for E. coli biologists, and for biologists who work with related microorganisms.

Enzyme Database http://www.expasy.ch/enzyme/

A repository of information relative to the nomenclature of enzymes. It is primarily based on the recommendations of the NomenclatureCommittee of the International Union of Biochemistry and Molecular Biology (IUBMB) and describes each type of characterized enzyme for which an EC (Enzyme Commission) number has been provided / 15-Jun-2000 (3705 entries)

GPCRDB http://www.gpcr.org/7tm/ (http://swift.embl-heidelberg.de/7tm/)

Information system for G protein-coupled receptors (GPCRs)

TIGR http://www.tigr.org/tdb & http://www/tigr.org/softlab

Sequenced genome data and software.

AceDB http://www.sanger.ac.uk/Software/Acedb/

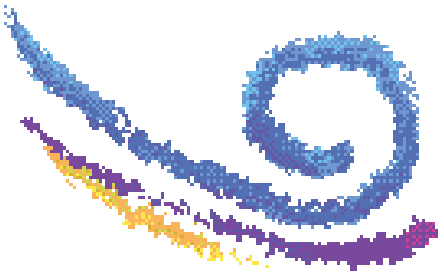
Acedb is a genome database system that provides a custom database kernel, with a non-standard data model designed specifically for handling scientific data flexibly, and a graphical user interface with many specific displays and tools for genomic data.

WIT http://wit.mcs.anl.gov/WIT2/

A www-based system to support the curation of function assignments made to genes and the development of metabolic models

dbSNP http://www.ncbi.nlm.nih.gov/SNP/

A database of single nucleotide polymorphisms



Database Links (CONT.)

DALI http://www2.ebi.ac.uk/dali/

A network service for comparing protein structures in 3D. You submit the coordinates of a query protein structure and Dali compares them against those in the Protein Data Bank.

VAST http://www.ncbi.nlm.nih.gov:80/Structure/VAST/vast.shtml

Protein structure neighbors in Entrez are determined by direct comparison of 3-dimensional protein structures with the VAST algorithm.

FSSP http://www2.ebi.ac.uk/dali/fssp/fssp.html

If you want to know the structural neighbours of a protein already in the Protein Data Bank, you can find them in the FSSP database

Scop http://scop.mrc-lmb.cam.ac.uk/scop/

Structural Classification of Proteins. 1.50 release / 10650 PDB Entries (29 Feb 2000)

FlyBase http://flybase.bio.indiana.edu:82/

Everything about Drosophila melanogaster

EMP (registration) http://wit.mcs.anl.gov/EMP/

Enzymes and metabolic pathways

JPRED http://jura.ebi.ac.uk:8888/

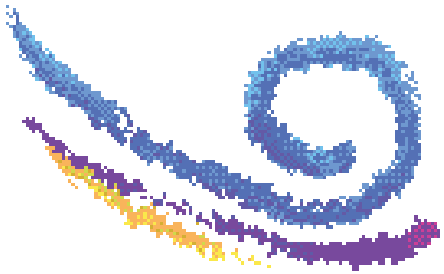
Consensus-based 2ndary structure prediction

E-motif http://motif.stanford.edu/emotif/

Pattern discovery from *aligned* sequences

PHYLIP http://evolution.genetics.washington.edu/phylip.html

The PHYLogeny Inference Package is a package of programs for inferring phylogenies (evolutionary trees).



Database Links (CONT.)

FASTA http://www2.ebi.ac.uk/fasta3/
Web-based interface for FASTA

BLAST http://www.ncbi.nlm.nih.gov/BLAST/
Web-based interface for Blast and its variants

Smith-Waterman http://www2.ebi.ac.uk/bic_sw/
Web-based interface for the Smith-Waterman algorithm

MSA http://www.ibc.wustl.edu/ibc/msa.html
The MSA multiple sequence alignment algorithm

CLUSTAL-W http://www.ibc.wustl.edu/msa/clustal.html
The CLUSTALW multiple sequence alignment algorithm

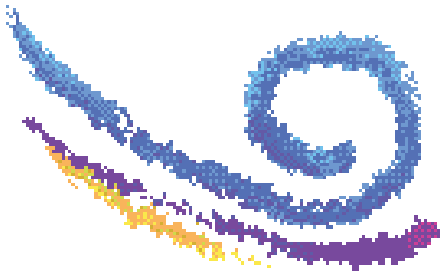
RasMol/Chime http://www.umass.edu/microbio/rasmol/
Molecular visualization freeware

PIMA http://dot.imgen.bcm.tmc.edu:9331/multi-align/Options/pima.html
Motif-based multiple sequence alignment based on pairwise comparisons

MolMol http://www.mol.biol.ethz.ch/wuthrich/software/molmol/
Molecule analysis, editing and display package

BOXSHADE http://www.ch.embnet.org/software/BOX_form.html
Tool for shading multiple sequence alignments

ESPript 1.9 http://www-pgm1.ipbs.fr:8080/cgi-bin/nph-ESPript_exe.cgi
Tool for coloring multiple sequence alignments



Database Links (CONT.)

GeneMark http://genemark.biology.gatech.edu/GeneMark/

HMM-based tool for discovering coding regions in prokaryotic genomes

GeneFinder http://dot.imgen.bcm.tmc.edu:9331/gene-finder/gf.html

Splice sites, Protein coding exons and Gene models construction, Promotor and poly-A search

ORFFinder http://www.ncbi.nlm.nih.gov/gorf/gorf.html

A graphical analysis tool which finds all open reading frames of a selectable minimum size in a user's sequence or in a sequence already in the database.

GeneQuiz http://jura.ebi.ac.uk:8765/ext-genequiz/

Highly automated analysis of biological sequences

PROWL http://prowl.rockefeller.edu/

A resource for protein chemistry and mass spectrometry

SAMBA http://www.irisa.fr/cosi/SAMBA/

SAMBA is a 128 processor array for speeding up the comparison of biological sequences. The hardware implements a parameterized version of the Smith and Waterman algorithm allowing the computation of local or global alignments with or without gap penalty.

MOTIF http://www.motif.genome.ad.jp/

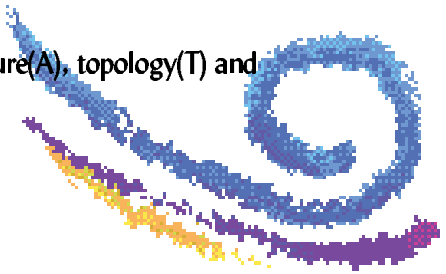
Automated search of motifs from various libraries in a sequence of interest

CATH http://www.biochem.ucl.ac.uk/bsm/cath/

A novel hierarchical classification of protein domain structures, which clusters proteins at four major levels, class(C), architecture(A), topology(T) and homologous superfamily (H)

MAGPIE http://genomes.rockefeller.edu/magpie/

MAGPIE Automated Genome Project Investigation Environment



Database Links (CONT.)

OWL http://www.biochem.ucl.ac.uk/bsm/dbbrowser/OWL/OWL.html

A non-redundant composite of 4 publicly-available primary sources: SWISS-PROT, PIR (1-3), GenBank (translation) and NRL-3D

dbEST http://www.ncbi.nlm.nih.gov/dbEST/index.html

A division of GenBank that contains sequence data and other information on "single-pass" cDNA sequences, or Expressed Sequence Tags, from a number of organisms. 4,334,336 entries by June 09, 2000.

DSSP http://swift.embl-heidelberg.de/dssp/ ???

The DSSP database is a database of secondary structure assignments (and much more) for all protein entries in the Protein Data Bank (PDB)

Grail http://compbio.ornl.gov/Grail-1.3/

Gene recognition and assembly internet link

PRATT http://www2.ebi.ac.uk/pratt/

Web server for a pattern discovery algorithm

PHD http://www.embl-heidelberg.de/predictprotein/predictprotein.html

A service for sequence analysis, and structure prediction.

MGD http://www.informatics.jax.org/

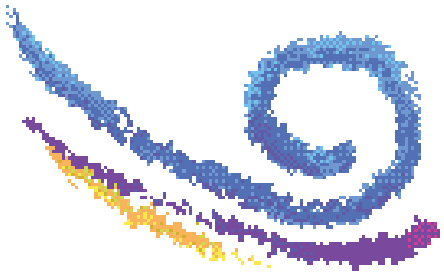
Mouse genome information

NTI Suite http://www.informaxinc.com/products/vectornti/downloads.html

Demo Program for NTI Viewer

Pedro (Coutinho)'s Site http://www.public.iastate.edu/~pedro/rt_all.html

Links to tools galore

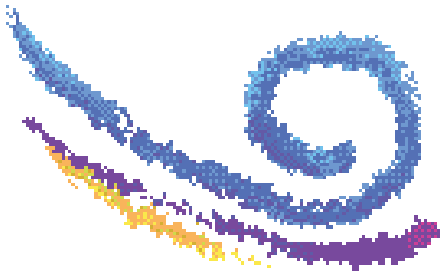


Useful Notation And Definitions From Computer Science

- $f(n) = O(g(n))$
  - f(n) is said to be $O(g(n))$ -- "big-Oh of g(n)" iff there exist constants c in R and n_0 in N such that $f(n) <= c * g(n)$ for all $n >= n_0$

- $f(n) = \Omega(g(n))$
  - f(n) is said to be $\Omega(g(n))$ -- "big-Omega of g(n)" iff there exist constants c in R and n_0 in N such that $f(n) >= c * g(n)$ for all $n >= n_0$

- $f(n) = \Theta(g(n))$
  - iff $f(n) = O(g(n))$ and $f(n) = \Omega(g(n))$



Recurrence Equation

- Defined in terms of … itself

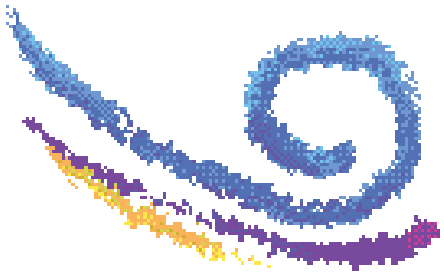
$$T(n) = f(T(1), T(2), T(3), \ldots, T(n-1), n)$$

Examples:

$T(1) = 1$
$T(n) = 2\,T(n-1) + 1$

$T(1) = 1$
$T(n) = T(n-1) + n$

$T(1) = 1/3$
$T(n) = T(n-1) + 1/(2n-1)/(2n+1)$

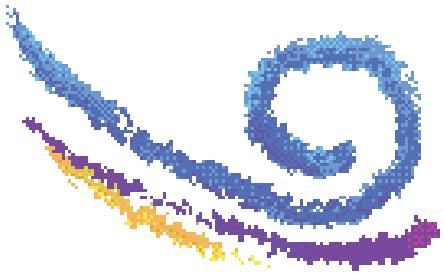


Recurrence Equation (cont.)

- The concept of "recursion"
  factorial (0) = 1
  factorial (n) = factorial (n-1) * n

```
int
factorial (int n)
{
if ( n == 0 ) {
   return(1) ;
   }
else {
   return ( n * factorial (n-1) ) ;
   }
}
```

Q: is there anything wrong with piece of code?



Sorting Numbers

- Input: a *S* set of *N* many real numbers
  Output: the same set in order of increasing value

  Theorem: "any algorithm that sorts n numbers by comparisons requires $\Omega(n \log n)$ comparisons"

- Algorithms: BubbleSort(S,N)
- * *QuickSort(S,N)

- Running times?

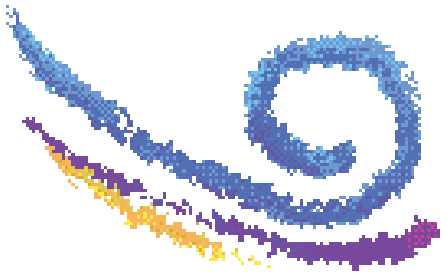
- "Efficient Algorithm": running time is a polynomial function of the input size N

Sorting Numbers (cont.)

QuickSort(S,N)
{
- if N=1 then return S

- pick random element r in S
- separate S into sets
  S_1 of elements that are < r,
  S_2 of elements = r, and S_3 of elements > r
- return the result of
  (QuickSort(S_1, $|S_1|$), S_2, QuickSort(S_3, $|S_3|$))

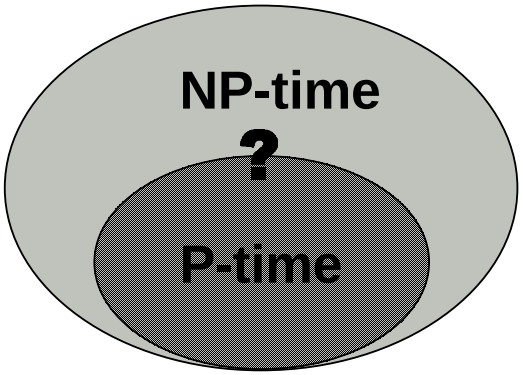
}



Useful Notation And Definitions From Computer Science

"Efficient algorithm" running time is O(p(n))

not "Efficient algorithm"



NP-complete problems

NP-hard problems: all optimization problems whose decision versions are NP-complete.

More Definitions

Graph

A set V of points (=vertices) and a set E of lines (=edges) that connect pairs of points.

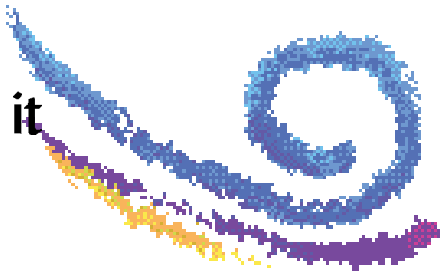
Notation: G= (V,E) with V={v_1, v_2, ..v_N} and E={(u,v) / u, v in V}

undirected graph: all edges are UNordered

directed graph: all edges (u,v) are ORrdered
u is the *tail* and v is the *head*

incident vertex/edge: an edge (u,v) is incident on the vertices u and v -- vertices u and v are incident on edge (u,v)

degree of a vertex: the number of vertices that are adjacent to it
(in-degree & out-degree in directed graphs)



More Definitions (cont.)

weighted: each edge is associated with a real number known as 'distance' , 'weight' or 'cost'

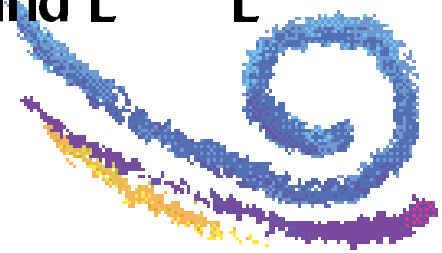
path: an ordered list (v1 , v2, ..vk) of vertices such that (vi, vi+1) is an edge of the graph

cycle in an UG: a path such that v1 =vk and no edge is repeated

cycle in a DG: a path such that k > 1 and v1 =vk

subgraph of a graph: a graph G'=(V',E') where V' V and E' E

acyclic: a graph without cycles



More Definitions (cont.)

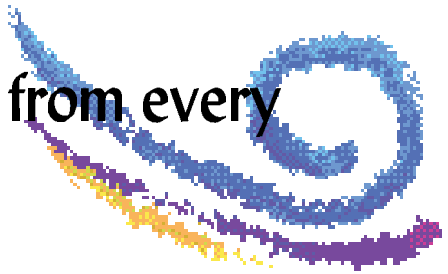
complete UG: a graph where for every pair u, v in V the edge (u,v) is in E

complete DG: a graph where for every pair u, v in V the edges (u,v) and (v,u) are in E

bipartite: a graph whose vertices can be separated into two sets V1 and V2 such that for every edge (u,v) in E we have u in V1 and v in V2

connected UG: iff every vertex of the graph can be reached from every other vertex of the graph

strongly connected DG: iff every vertex can be reached from every vertex



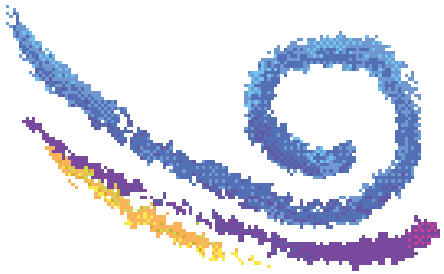
More Definitions (cont.)

weakly connected DG: / disregard directions

not-connected DG: / if neither strongly nor weakly

interval graph (undirected): begin with a collection of intervals on the real line; create a vertex for each interval in the collection to build V; for any two intervals u and v with non-zero intersection enter (u,v) in E

adjacency matrix of a graph: a $|V| \times |V|$ matrix M with M(i,j) = 1 if (vi, vj) is in E, 0 otherwise. If the graph is weighted M(i,j) is the weight of the respective edge



More Definitions (cont.)

Tree: A directed acyclic graph that a) has a root vertex that no edges enter, b) every vertex other than the root has one edge entering it, and c) there is a unique path from the root to every vertex.

leaf: a vertex with no outgoing edges

parent & child: if (u,v) is in E then u (resp. v) is the parent (resp. child) of v (resp. u)

depth of a vertex: the length of the path from the root to the vertex

height of a vertex: the length of the longest path from the vertex to any leaf

least common ancestor:

More Definitions (cont.)

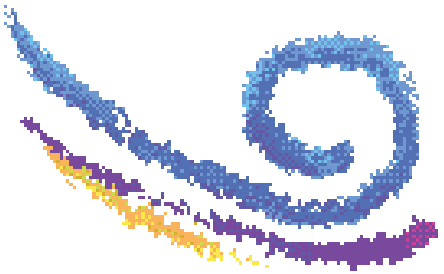
Undirected (rooted) Tree: A connected, undirected acyclic graph with one vertex distinguished as the root.

Graph Traversal: Traverse (visit) all of the vertices of the graph.

'Popular' Traversal Schemes:

Depth-First

Breadth-First



Spanning Tree

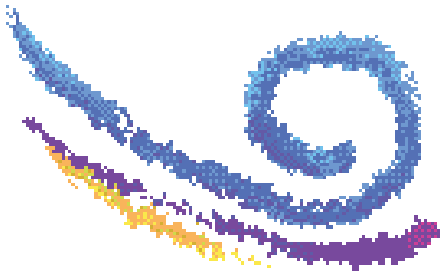
Definition: Let G=(V,E) be an undirected, connected graph. Its spanning tree is an undirected tree S=(V,T) and its cost is the sum of the weights of the edges in T.

Minimum Cost Spanning Tree

The Minimum Cost Spanning Tree Property

Prim's algorithm: Make the greedy choice

Running time: $O(n^2)$



Tree Traversals

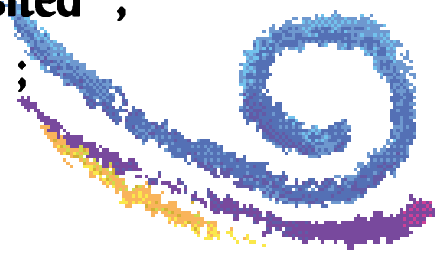
- Popular traversals: DFS and BFS

Depth First Traversal

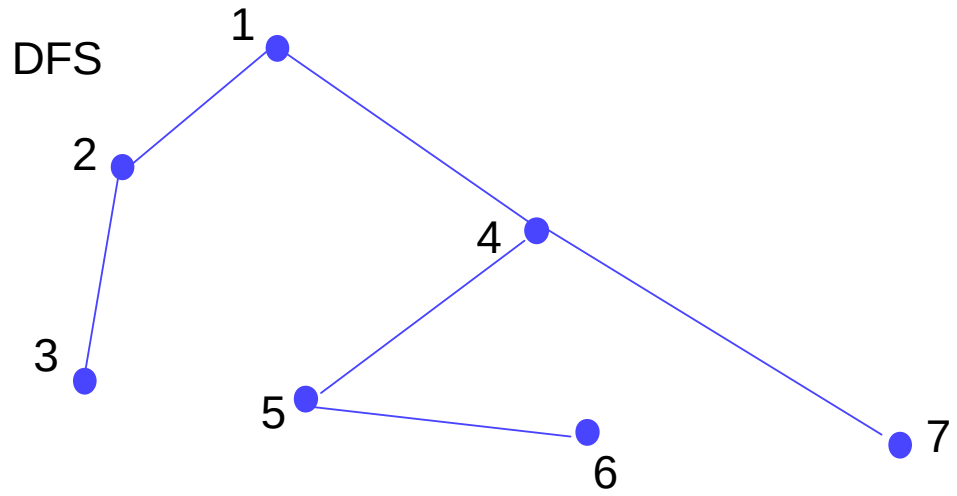
```
dfs(v) {
mark v as "visited" ;
for each vertex w that is adjacent to v
    if ( w has not been "visited" )
       dfs(w) ;
    end-if
end-for
}
```

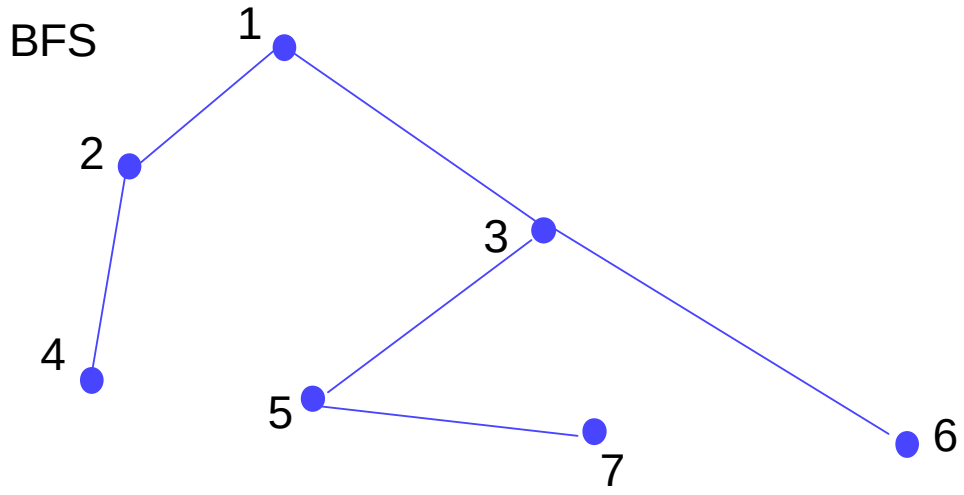
Breadth First Traversal

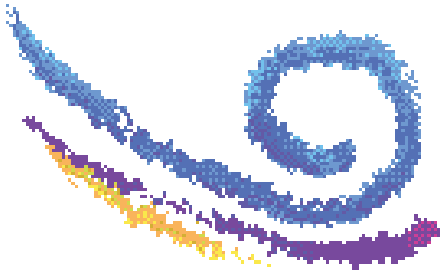
```
    L <- {v} ;

bfs(L) {
if ( L is not empty )
    let f be the first element of L ;
    mark f as "visited" ;
    remove f from L ;

    for each vertex w that is adjacent to f
        if ( w has not been "visited" )
           mark w as "visited" ;
           append w to L ;
        end-if
    end-for
```



Tree Traversals - Example







Simple And Otherwise

Simple Problems

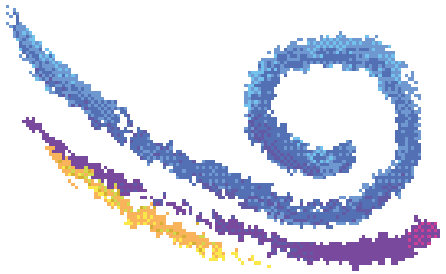
- Given a DG/UDG, find a cycle that includes every edge of the graph only once (Eulerian graph)
- Given an UDG that is connected find a minimum spanning tree for it
- Given an UDG find a maximum cardinality subset of the edges such that no two edges share a vertex

Seemingly Simple Problems

- Given a DG/UDG, find a cycle that includes every vertex of the graph only once - except for first/last vertex (Hamiltonian graph)
- Given an UDG with cost on each edge, find a Hamiltonian cycle of minimum cost (TSP)
- Given an UDG find the minimum number of colors needed to color it so that no two adjacent vertices have the same color

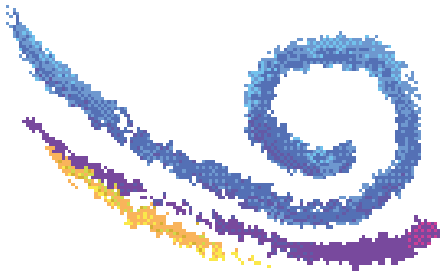
Maps

- Genetic Linkage map
  - 10-100M bp
  - order and relative distance among genes
- Physical Map
  - 0.1-1M bp
  - maps showing actual distance among genes
- Sequencing
  - 1-10K bp
  - actual contents of genes



Maps (cont.)

- Full DNA — 10-100 Mbp
  - cut and clone into overlapping YAC clones — 0.1-1 Mbp
    - cut and clone into overlapping cosmid clones — 10-50 Kbp
      - sequence by shotgun — 1 Kbp



Maxam-Gilbert Sequencing Method

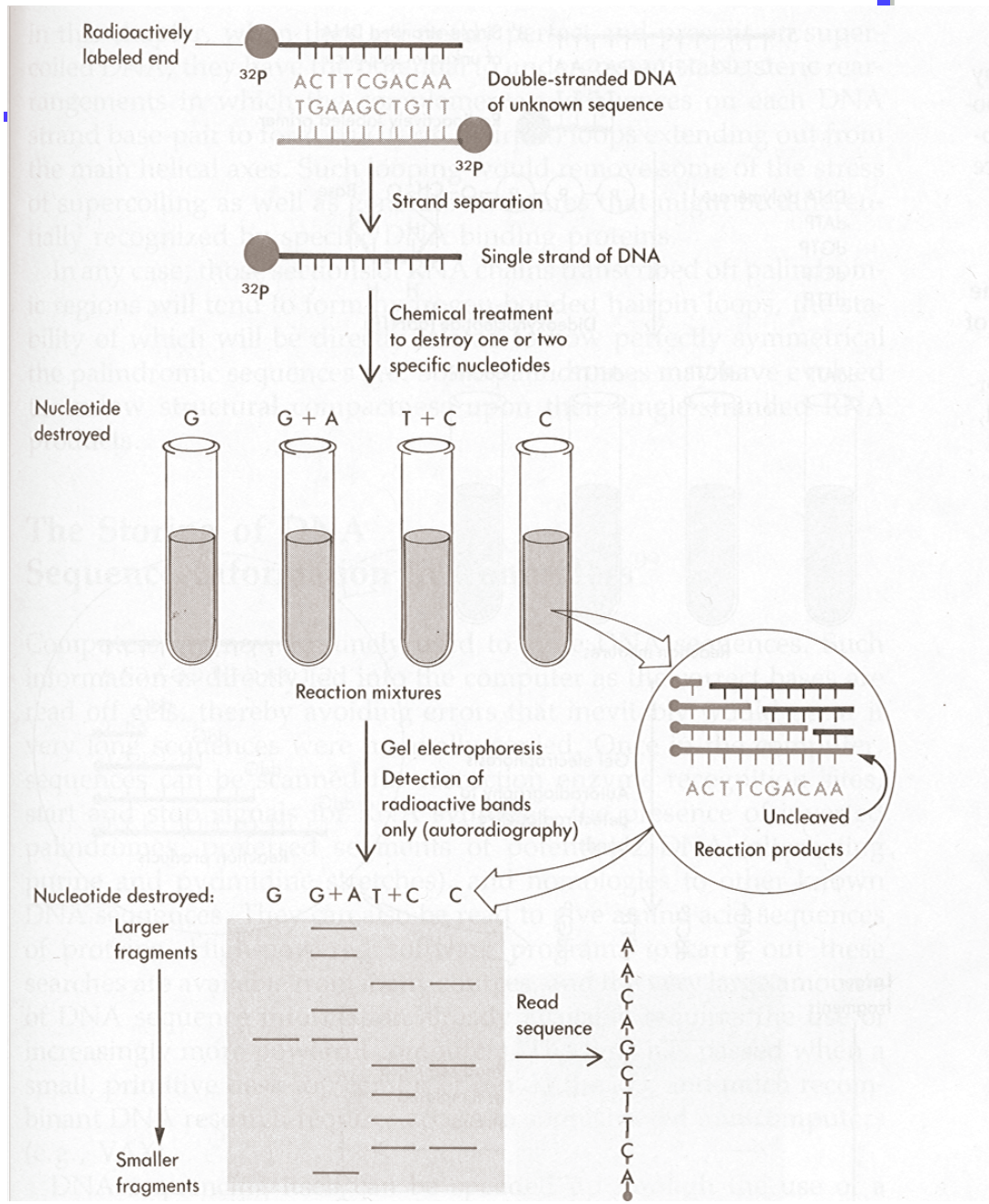


Figure 9-44
DNA-sequencing method developed by Maxam and Gilbert. This method uses chemical reagents to destroy specific nucleotide bases and thus break the DNA molecule at specific sites. First the strands of the DNA molecule are labeled radioactively at one end (usually the 5′ end), and the two strands are separated (only one will be sequenced). Then aliquots of the chosen strand are treated with four different chemical reagents that break the strand at one or two specific nucleotides; the treatment is limited so that at most a single residue of the susceptible base(s) in the molecule will react. Thus, in each reaction mixture, a nested set of radioactive fragments is generated, as shown here for only the reaction mixture that destroys C residues. Finally, gel electrophoresis is used to separate the products of each reaction by size. The pattern of radioactive bands seen on X-ray film immediately reveals the sequence.

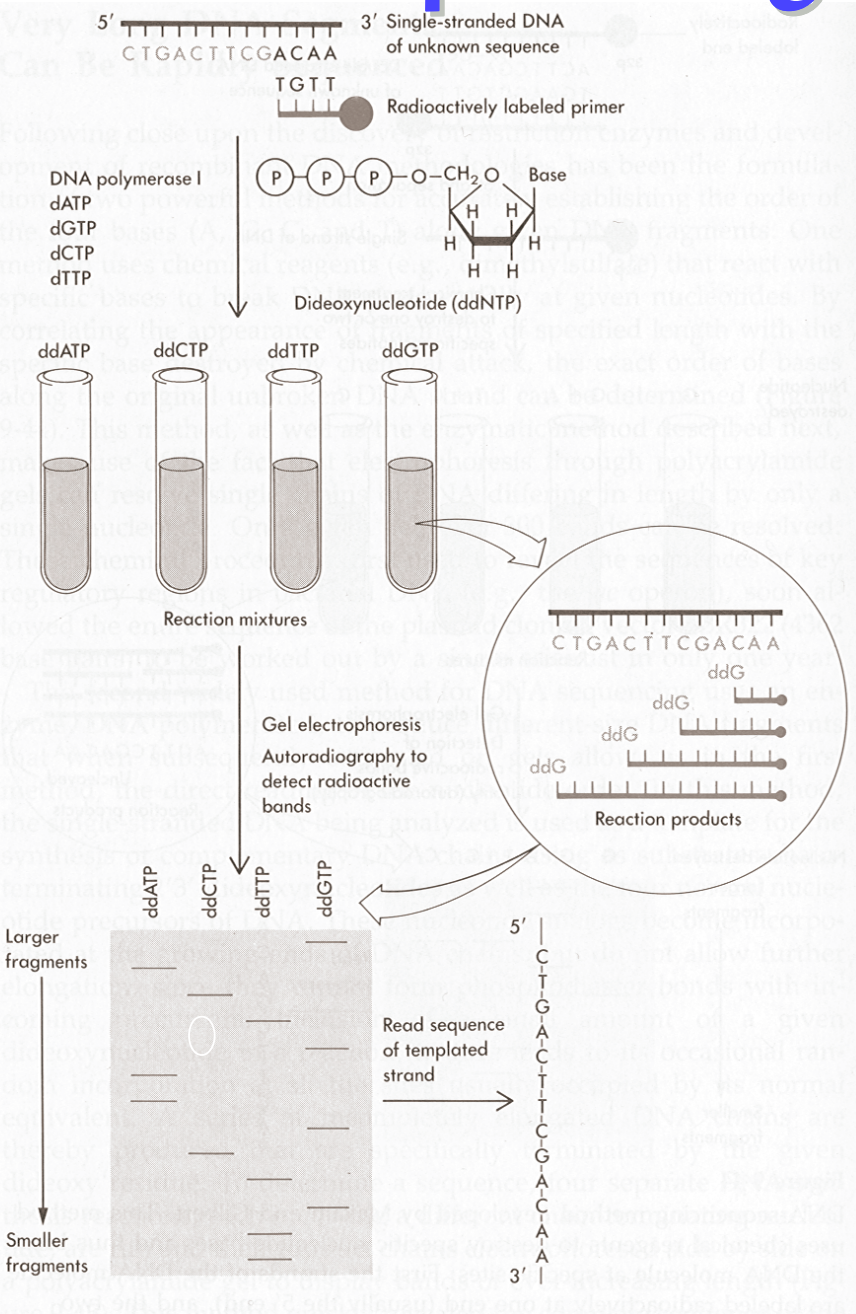
Maxam, A. M. and Gilbert, W. (1977) "A new method for sequencing dna" Proc. Natl. Acad. Sci. USA 74, 560-564.

Maxam, A and Gilbert, W. (1980) Sequencing end-labeled dna with base-specific chemical cleavages. Methods of Enzymology, 65, Part 1:499-560.

Figure from: Molecular Biology Of The Gene 4th edition Watson/Hopkins/Roberts/Steitz/Weiner pp 275

Sanger-Coulson Sequencing Method

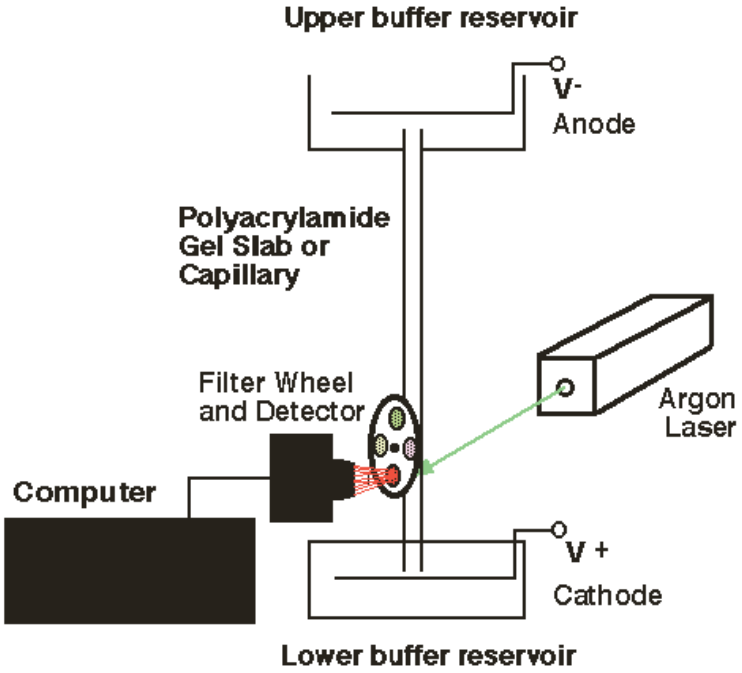
Figure 9-45
DNA-sequencing method developed by Sanger. A dideoxynucleotide is incorporated into a growing DNA strand, subsequently stopping chain growth, since it cannot form a phosphodiester bond with the next incoming nucleotide. Four different reactions are run, each with a different dideoxynucleotide. The products of each reaction are a series of incompletely elongated segments, which are separated by gel electrophoresis. As in the Maxam-Gilbert method, the sequence can be read from the bands produced in the gel.



Sanger F, Nicklen S, Coulson AR 1977b. DNA sequencing with chain-terminating inhibitors. Proc Natl Acad Sci USA 74: 5463-5467.

Sanger F, Coulson AR, Hong GF, Hill DF, Petersen GB 1982. Nucleotide sequence of bacteriophage lambda DNA. J Mol Biol 162:729-773

Fluorescence



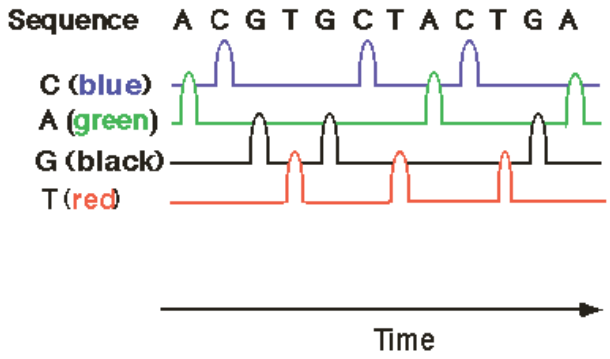
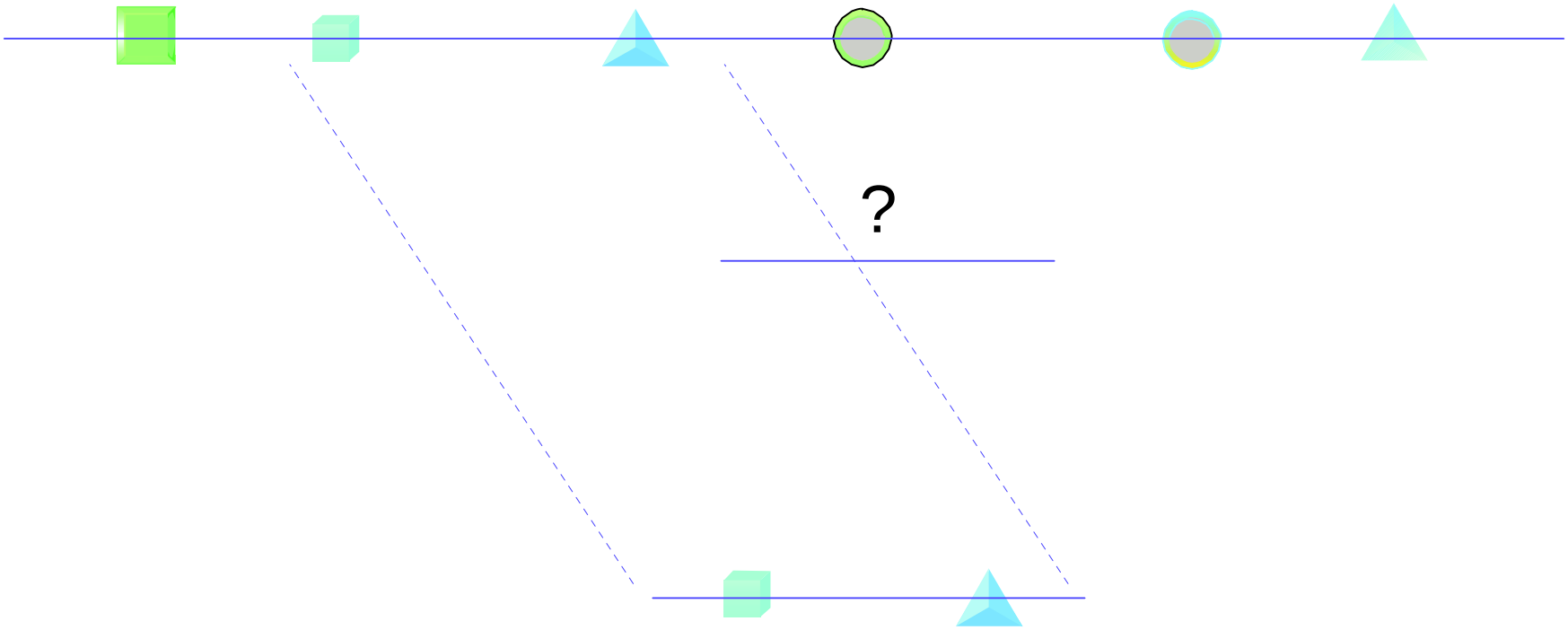
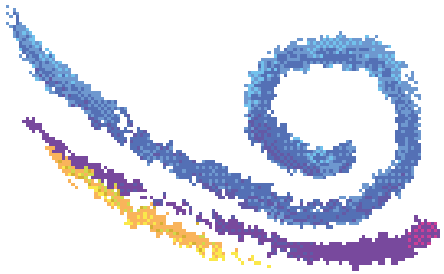


Figure from: http://dna.ctandct.com/PGG/PGG.html

Physical Maps

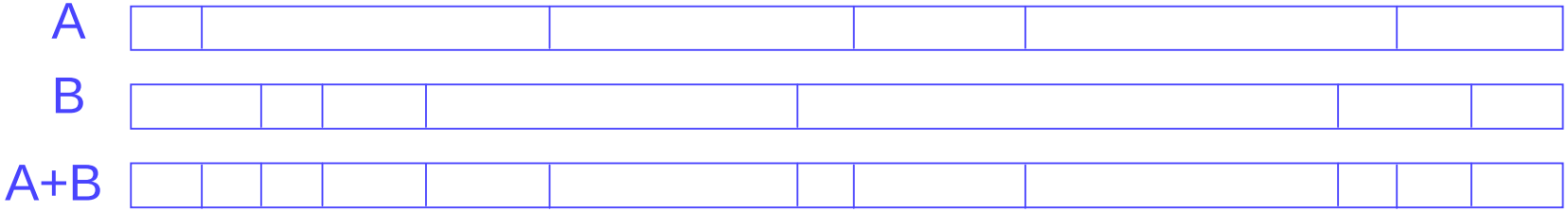


- fingerprints



How To Get Fingerprints

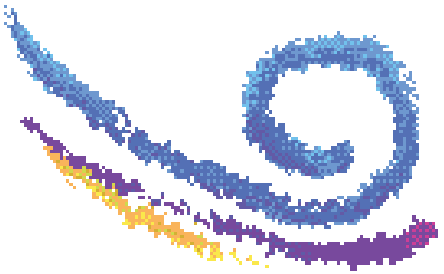
- Restriction Site Mapping
  - fingerprint is the length of the fragment
  - double digest



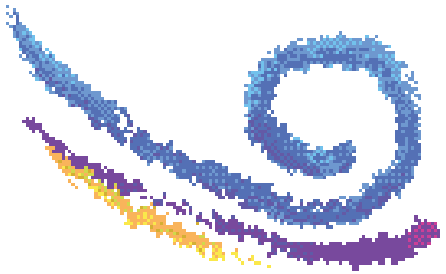
  - partial digest
  - Errors:
    - inaccuracy in measuring lengths
    - fragments too short

How To Get Fingerprints (cont.)

- Hybridization Mapping
  - *probes & clones*
  - fingerprint is the set of probes hybridizing to the clone
  - Errors:
    - false positives
    - false negatives
    - chimeric clones



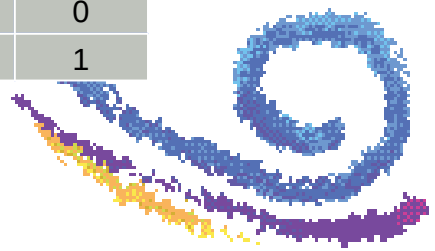
- interval graphs



From Hybridization To Maps

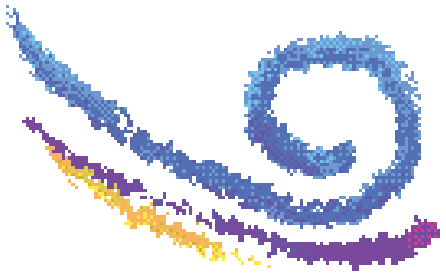
- Assumptions:
  - probes are "unique"
  - there are no errors
  - all "clones x probes" have been carried out

	P1	P2	P3	P4	P5	P6	P7	P8	P9
C1	1	1	0	1	1	0	1	0	1
C2	0	1	1	1	1	1	1	1	1
C3	0	1	0	1	1	0	1	0	1
C4	0	0	1	0	0	0	0	1	0
C5	0	0	1	0	0	1	0	0	0
C6	0	0	0	1	0	0	1	0	0
C7	0	1	0	0	0	0	1	0	0
C8	0	0	0	1	1	0	0	0	1



From Hybridization To Maps (cont.)

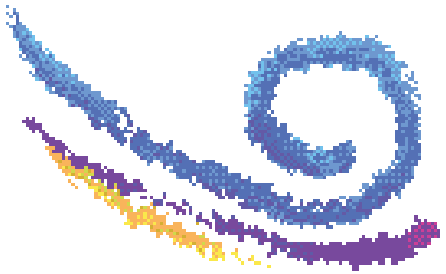
	P1	P2	P3	P4	P5	P6	P7	P8	P9
C1	**1**	**1**	**1**	**1**	**1**	**1**	0	0	0
C2	0	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**
C3	0	**1**	**1**	**1**	**1**	**1**	0	0	0
C4	0	0	0	0	0	0	0	**1**	**1**
C5	0	0	0	0	0	0	**1**	**1**	0
C6	0	0	0	**1**	**1**	0	0	0	0
C7	0	0	0	0	**1**	**1**	0	0	0
C8	0	**1**	**1**	**1**	0	0	0	0	0



From Hybridization To Maps (cont.)

- pick any two rows i, j
- let S_i be the set of columns where there is 1's in row i

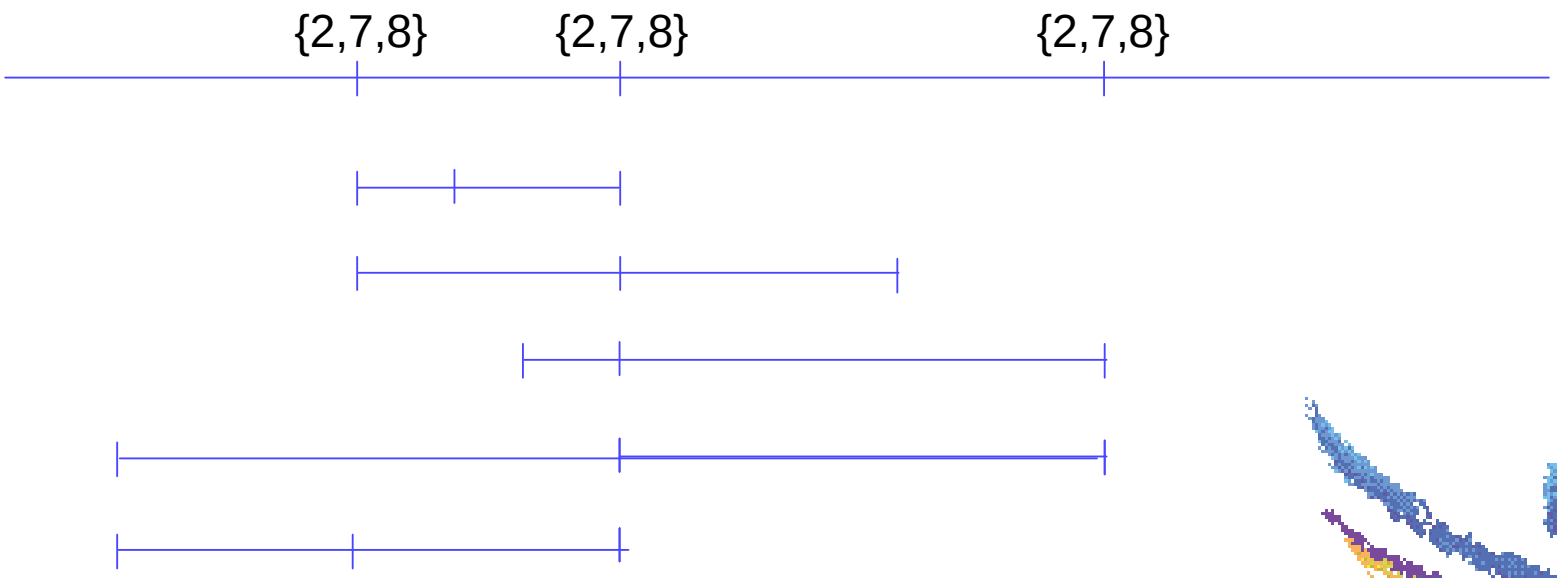
- cases:
  - S_i intersection S_j = empty
  - S_i subset of S_j (or vice versa)
  - non-zero intersection



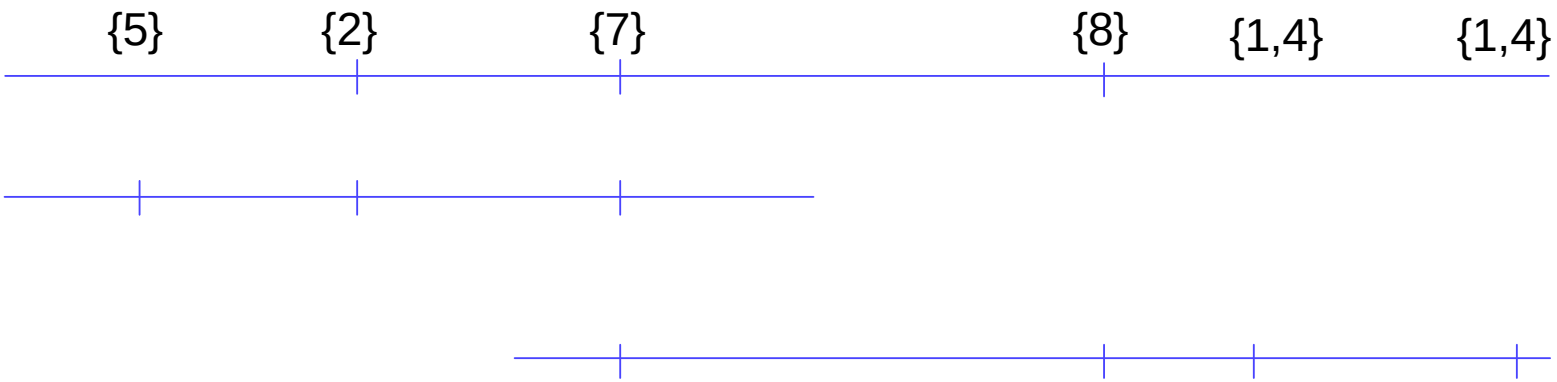
From Hybridization To Maps (cont.)

let's work with this specific example:

	P1	P2	P3	P4	P5	P6	P7	P8
C1	0	1	0	0	0	0	1	1
C2	0	1	0	0	1	0	1	0
C3	1	0	0	1	0	0	1	1



From Hybridization To Maps (cont.)



From Hybridization To Maps (cont.)

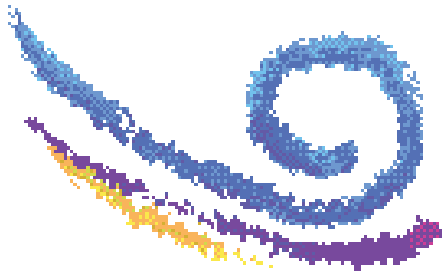
back to the original example:

C1	**1**	**1**	**1**	**1**	**1**	**1**	0	0	0
C2	0	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**

C3	...	**1**	**1**	**1**	**1**	**1**	...
C4							
C5							

sub
sum
ed

C6	...	0	0	**1**	**1**	0	...
C7	...	0	0	0	**1**	**1**	...
C8	...	**1**	**1**	**1**	0	0	...

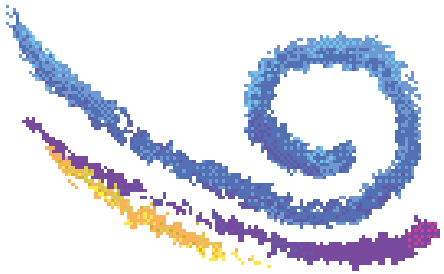


From Hybridization To Maps (cont.)

- Summing it up:
  - build a uDG with one vertex for each row
  - an edge connects two vertices if the respective S_i's intersect (only!)

<u>FIX columns within a group</u>
- traverse graph in DF order
- at every vertex apply Place(u, v, w) (see Setubal/Meidanis Ch. 5)

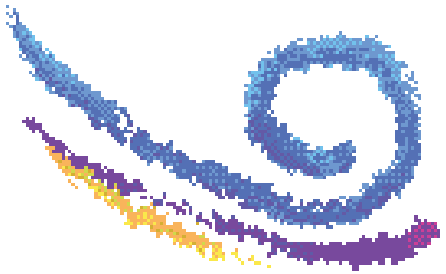
<u>Join groups</u>
- build a DG with an edge between groups A and B iff all of B's rows are subsumed by some row in A
- process vertices in topological order gluing components together



Fragment Assembly

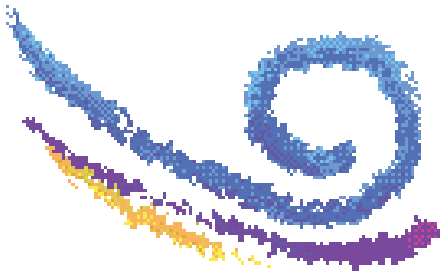
- We want to sequence entire molecule directly
- ... but we cannot / we can only have small-size fragments

- Start with "shotgun" and generate large number of fragments in 200-700 bp range
- Use estimated size of *target* and overlap information as guide
- Report "consensus" sequence



Fragment Assembly (cont.)

- Problems:
  - Errors
    - base calling / chimeric frags. / contamination
  - Unknown orientation
  - Repeated regions
    - AXBXCXD, AXBYCXDYE, X...X
  - No coverage



Fragment Assembly (cont.)

- SCS:

  Definition: Given a collection F of strings, find the shortest possible string S s.t. for every f in F, S is a superstring of f.

  - does not allow for experimental errors
  - orientation must be known
  - if repeats present, answer will be *shorter*

NP-hard

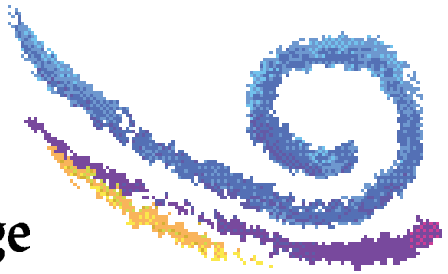
- Reconstruction

  Definition: Given a collection F of strings and a tolerance e in $[0,1]$ find the shortest possible string S s.t. for every f in F

$$\min(d(f,S), d(\underline{f},S)) <= e\,|f|$$

  - can cope with errors and orientation
  - cannot handle chimeric frags. / repeats / lack of coverage

NP-hard



Fragment Assembly (cont.)

- MultiContig

  Definition: Given a collection F of string, an integer t and a tolerance e in [0,1] find the minimum number of sub-collections C_i $1 <= i <= k$ s.t. every C_i admits a t-contig with e-consensus

  NP-hard

  - models errors, orientation and gaps
  - cannot use size of target
  - partial success with repeats