# Today's Lecture

- (Finding exact matches in sequences using suffix arrays)
- Algorithm generalities / complexity
- Directed graphs, DAGs

# Finding perfectly matching subsequences of a sequence

- Idea (*much* more efficient than 'brute force' approach):
  - *suffix array* (Manber & Myers, 1990)
  - make list of pointers to all positions in sequence
  - lexicographically sort list of strings that are pointed to
  - process the list: adjacent entries are "maximally agreeing"

# Suffix array step 1: List of Pointers to Suffixes

**ACCTGCACTAAACCGTACACTGGGTTCAAGAGATTTCCC**

$p_1$ ACCTGCACTAAACCGTACACTGGGTTCAAGAGATTTCCC
$p_2$ CCTGCACTAAACCGTACACTGGGTTCAAGAGATTTCCC
$p_3$ CTGCACTAAACCGTACACTGGGTTCAAGAGATTTCCC
$p_4$ TGCACTAAACCGTACACTGGGTTCAAGAGATTTCCC
$p_5$ GCACTAAACCGTACACTGGGTTCAAGAGATTTCCC
$p_6$ CACTAAACCGTACACTGGGTTCAAGAGATTTCCC
$p_7$ ACTAAACCGTACACTGGGTTCAAGAGATTTCCC
$p_8$ CTAAACCGTACACTGGGTTCAAGAGATTTCCC
$p_9$ TAAACCGTACACTGGGTTCAAGAGATTTCCC
$p_{10}$ AAACCGTACACTGGGTTCAAGAGATTTCCC
$p_{11}$ AACCGTACACTGGGTTCAAGAGATTTCCC
$p_{12}$ ACCGTACACTGGGTTCAAGAGATTTCCC

⋮

# Suffix array step 2: View as Strings to be Compared

**ACCTGCACTAAACCGTACACTGGGTTCAAGAGATTTCCC**

$p_1$ ACCTGCACTAAACCGTACACTGGGTTCAAGAGATTTCCC
$p_2$ CCTGCACTAAACCGTACACTGGGTTCAAGAGATTTCCC
$p_3$ CTGCACTAAACCGTACACTGGGTTCAAGAGATTTCCC
$p_4$ TGCACTAAACCGTACACTGGGTTCAAGAGATTTCCC
$p_5$ GCACTAAACCGTACACTGGGTTCAAGAGATTTCCC
$p_6$ CACTAAACCGTACACTGGGTTCAAGAGATTTCCC
$p_7$ ACTAAACCGTACACTGGGTTCAAGAGATTTCCC
$p_8$ CTAAACCGTACACTGGGTTCAAGAGATTTCCC
$p_9$ TAAACCGTACACTGGGTTCAAGAGATTTCCC
$p_{10}$ AAACCGTACACTGGGTTCAAGAGATTTCCC
$p_{11}$ AACCGTACACTGGGTTCAAGAGATTTCCC
$p_{12}$ ACCGTACACTGGGTTCAAGAGATTTCCC

⋮

# Suffix array step 3: Sort the Pointers Lexicographically

**ACCTGCACTAAACCGTACACTGGGTTCAAGAGATTTCCC**

| | |
|---|---|
| $p_{10}$ | AAACCGTACACTGGGTTCAAGAGATTTCCC |
| $p_{11}$ | AACCGTACACTGGGTTCAAGAGATTTCCC |
| $p_{28}$ | AAGAGATTTCCC |
| $p_{17}$ | ACACTGGGTTCAAGAGATTTCCC |
| $p_{12}$ | ACCGTACACTGGGTTCAAGAGATTTCCC |
| $p_{1}$ | ACCTGCACTAAACCGTACACTGGGTTCAAGAGATTTCCC |
| $p_{7}$ | ACTAAACCGTACACTGGGTTCAAGAGATTTCCC |
| $p_{19}$ | ACTGGGTTCAAGAGATTTCCC |
| $p_{29}$ | AGAGATTTCCC |
| $p_{31}$ | AGATTTCCC |
| $p_{33}$ | ATTTCCC |
| $p_{27}$ | CAAGAGATTTCCC |
| | ⋮ |

# Finding Matching Subsequences Using the Sorted List of Pointers

- Perfectly matching subsequences
  - (more precisely – the pointers to the starts of those subsequences)

  are "near" each other in the sorted list
- For a given subsequence, a *longest* perfect match to it is *adjacent* to it in the sorted list
  - (there may be other, equally long matches which are not adjacent, but they are nearby).

# (Average Case) Complexity Analysis

- If $N$ = sequence length, sorting can be done with
  - $O(N\log(N))$ comparisons,
  - each requiring $O(\log(N))$ steps on average,

  for an overall complexity of $O(N(\log(N))^2)$.
  - (Processing the sorted list requires an additional $O(N)$ steps which does not affect the overall complexity).
- Manber & Myers (1990) have more efficient algorithm ($O(N\log(N))$)
- several $O(N)$ algorithms are now known – but the best implementations are not as fast as $O(N\log(N))$ algorithms, even for very large genomes!!
- $\exists$ other, older $O(N)$ methods ('suffix trees'), but these are
  - much less space efficient,
  - harder to program, and
  - (probably) slower in practice

- HW #1 asks you to apply this algorithm to find:
  - longest perfectly matching subsequences in 2 genomic sequences & their reverse complements.
- much faster than an $O(N^2)$ algorithm (e.g. Smith-Waterman, or even BLAST), *but*
- limited to finding *exact* matches

# Algorithms – Some General Remarks

- The most widely used algorithms are the oldest
  - e.g. sorting lists, traversing trees, dynamic programming.

The challenge in CMB is usually *not* finding *new* algorithms, but rather

  - finding ***biologically appropriate applications*** of old ones.

- Often prefer
  - suboptimal but easy-to-program algorithm over more optimal one
  - or space-efficient algorithm over time-efficient one.
- *Probabilities* are important in
  - interpreting results
  - guiding search

The most powerful analyses generally involve probabilistic models, rather than deterministic ones.

# Genomes are big but computers are fast!

- Typical laptop clock speed: ~ 1 Ghz
  - Potentially billions of CPU instructions / sec
- Important practical consideration in dealing with genome-scale data sets: compared to CPU operations,
  - *non-cache memory accesses* are very slow (100s of cycles)
  - *disk accesses* are even slower (1000s of cycles)
  - for both, random (non-sequential) accesses are much slower than sequential accesses

# Algorithmic Complexity

- Basic questions about an algorithm:
  - how long does it take to run?
  - how much space (RAM or disk space) does it require?
- Would like precise function $f(N)$, e.g.

$$f(N) = .05\ N^3 + 50.7\ N^2 + 6.03\ N$$

for

  - running time in secs, or
  - space in kbytes,

as function of the size $N$ of input data set.

- But
  - tedious to derive &
  - depends on (often uninteresting – though important!) hardware & software implementation details.

# Algorithmic Complexity (cont'd)

- Instead, more customary to give "the" *asymptotic complexity*, i.e. expression $g(N)$ such that

$$C_1 g(N) < f(N) < C_2 g(N)$$

for some constants $C_1$ and $C_2$, and $N$ large enough.

- This is written $O(g(N))$, where notation $O()$ means "up to an unspecified multiplicative constant".
  - e.g. for the $f(N)$ above, the dominating term for large $N$ is $.05\ N^3$, so
    - can take $g(N) = N^3$
    - asymptotic complexity = $O(N^3)$.

# Algorithmic Complexity (cont'd)

- Can be misleading, since
  - for small $N$ a different term may dominate
    - (e.g. $2^d$ term in above example much more important for $N < 1000$)
  - size of constant may be quite important
    - (big difference between .05 and 5,000,000!)
    - e.g. BLAST and Smith-Waterman both $O(N^2)$, but size of constant enormously different
- *but* very useful as rough guide to performance.

# Algorithmic Complexity (cont'd)

- Cache misses (non-cache memory accesses) and disk accesses often dominate running time, yet are 'invisible' to complexity analysis (because affect constant factor only)

# Algorithmic Complexity (cont'd)

- Another limitation to complexity analysis:
  - time or space requirement may depend on specific characteristics of input data.
- Usually give "worst case" complexity
  - applies to the worst data set of a given size,

*but*

  - in biological situations the *average biologically occurring case* is
    - more relevant
    - often much easier than worst case (which may never arise in practice), or even "average case" in some idealized sense.

# Algorithmic Complexity (cont'd)

- Proof that a problem is *NP-hard*
  - (has complexity very likely greater than any polynomial function of *N* and therefore effectively unsolvable for large *N*)

can be useful in guiding search for more efficient algorithms

*but* can also be misleading, since

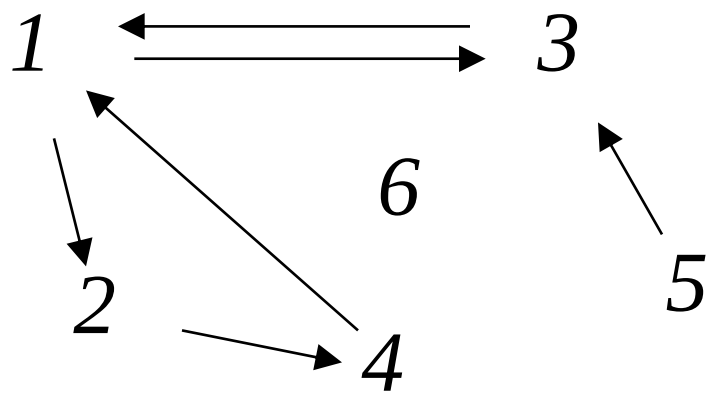
- we need *some* solution anyway, for data sets occurring in practice
- average *biologically relevant* case may be quite manageable

# Directed Graphs

- A *directed graph* is a pair $(V, E)$ where
  - $V$ is a finite set of *vertices*, or *nodes*.
  - $E$ is a set of ordered pairs (called *edges*) of vertices in $V$.
- An edge $(v_i, v_j)$ is said to *leave* $v_i$ and to *enter* $v_j$.
  - ($v_i$ and $v_j$ are vertices)
- *in-degree* of a vertex = # edges entering it;
- *out-degree* = # edges leaving it.

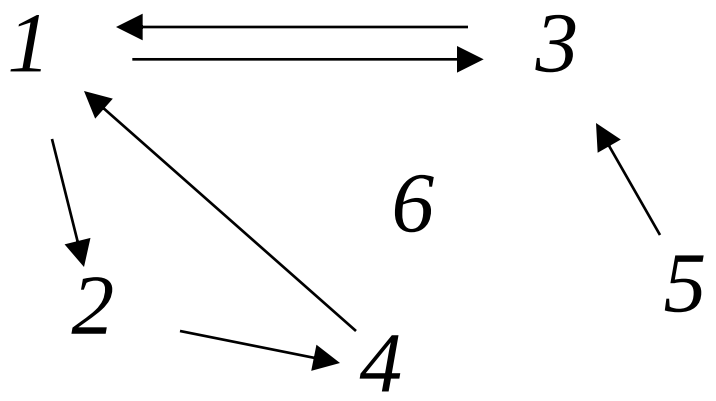
# Example:

- $V = \{1,2,3,4,5,6\}$,
- $E = \{(1,2), (1,3), (2,4), (4,1), (5,3), (3,1)\}$
- Vertex *3* has in-degree 2 and out-degree 1.



# Paths and Cycles

- A *path* of *length k* in *G from u* to *u'* (vertices) is
  - a sequence $P$ of vertices $(v_0, v_1, \ldots, v_k)$ such that
    - $v_0 = u$,
    - $v_k = u'$, and
    - $(v_{i-1}, v_i)$ is an edge for $i = 1,2, \ldots, k$.
- A path can have length 0.
- We write $|P| = k$.
- A *cycle* is a path of length $\geq 1$ from a vertex to itself.
- In example at right,
  - (*1*,*2*,*4*) is a path,
  - (*1*,*3*,*5*) is not, and
  - (*1*,*2*,*4*,*1*) and (*1*,*3*,*1*) are cycles.



# Paths and Cycles (cont'd)

- Can join
  - any path ($u$, ... , $v$) from $u$ to $v$, to
  - any path ($v$, ... , $w$) from $v$ to $w$

  to get a path ($u$, ... , $v$, ... , $w$) from $u$ to $w$.

# DAGs

- A *directed acyclic graph* (DAG) is a directed graph with no cycles.
- In a DAG, for distinct nodes $v_i$ and $v_j$, we say
  - $v_i$ is a *parent* of $v_j$, and $v_j$ is a *child* of $v_i$, if
    - there is an edge $(v_i, v_j)$
  - $v_i$ is an *ancestor* of $v_j$, and $v_j$ is a *descendant* of $v_i$, if
    - there is a path from $v_i$ to $v_j$
- In a DAG the length of a path cannot exceed $|V| - 1$,
  - (where $|V|$ = total # vertices in graph)

  because
  - in a path of length $\geq |V|$,
    - at least one vertex $v$ would have to appear twice in the path;
  - but then there would be a path from $v$ to $v$, i.e. a cycle.

# Structure of DAGs

- Define the *depth* of a node $v$ in $V$ as:
  - the length of the longest path ending at $v$;

  by above, the depth is well-defined and $\leq |V| - 1$.
- *Every descendant $w$ of a node $v$ has higher depth than $v$*: If
  - $(u, \ldots, v)$ is path of length $n$ = depth($v$) ending at $v$, and
  - $(v, \ldots, w)$ is path from $v$ to $w$,

  then $(u, \ldots, v, \ldots, w)$ is a path of length $> n$ ending at $w$, so depth($w$) $> n$.

# Structure of DAGs (cont'd)

- *Every node v of positive depth has a parent of depth exactly one less*:
  - Let ($u$, ... , $v'$, $v$) be path of length $n$ = depth($v$) ending at $v$.
  - Then $v'$ is a parent of $v$.
  - Since ($u$, ... , $v'$) has length $n - 1$, depth($v'$) $\geq n - 1$.
  - Since also depth($v'$) $< n$ (because $v$ is a descendant of $v'$), depth($v'$) is exactly $n - 1$.
- *The nodes on any path are of increasing depth*.