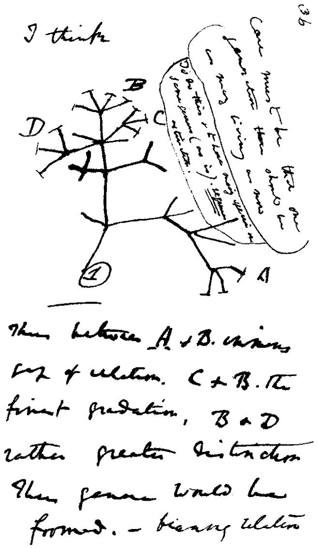
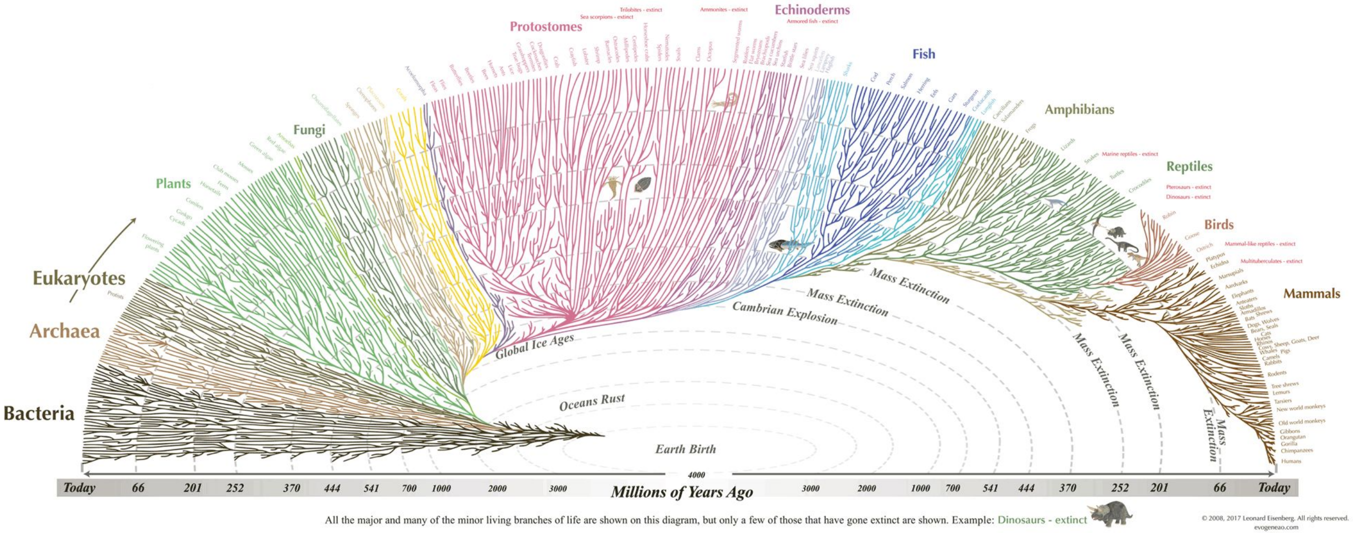
Week 4: Sequence alignment

- Global alignment
  - Dynamic programming
  - Needleman-Wunsch algorithm
- Local alignment
  - Smith-Waterman algorithm
  - BLAST

Sequence evolution

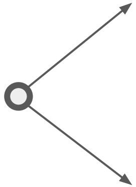




deletion mutation insertion

ACATGGTCA → AC*TGGTCA → ACTG**A**TCA → ACTGAT**T**CA

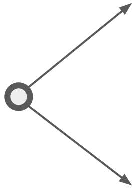
Evolutionary time →



human
ACTGATTCA

mouse
ACGCATCA

Sequence alignment



human
ACTGATTCA

mouse
ACGCATCA

Sequences can be aligned by allowing for **gaps** and **mismatches**.

ACTGATTCA	ACTGATTCA	ACTG-ATTCA
ACGCA-TCA	AC-GCATCA	AC-GCAT-CA

Which alignment is correct?

A scoring scheme:
- Match: 2
- Mismatch: -3
- Gap: -2

We will come back to this!

2+2-3-3+2-2+2+2+2 = 4	2+2-2+2-3-3+2+2+2 = 4	2+2-2+2-2+2+2-2+2+2 = 8

Alignment is gap placement.

How many possible alignments?

Dynamic programming

Solve a given complex problem by:

1. Breaking it into **<u>subproblems</u>** and
2. Storing the results of subproblems to avoid computing the same results again.

Two key properties of a problem that suggest that the given problem can be solved using DP.

1. Overlapping Subproblems
    - Given problem can be recursively broken down into subproblems that can be related to each other. That is, total no. of subproblems is polynomial.
2. Optimal Substructure
    - The optimal solution can be produced by combining optimal solutions of subproblems.

Richard Bellman

Optimal decision processes, involved time series & planning - thus 'dynamic' & 'programming'.

“It's impossible to use the word dynamic in a pejorative sense”; DP was “something not even a Congressman could object to.”

Dynamic programming

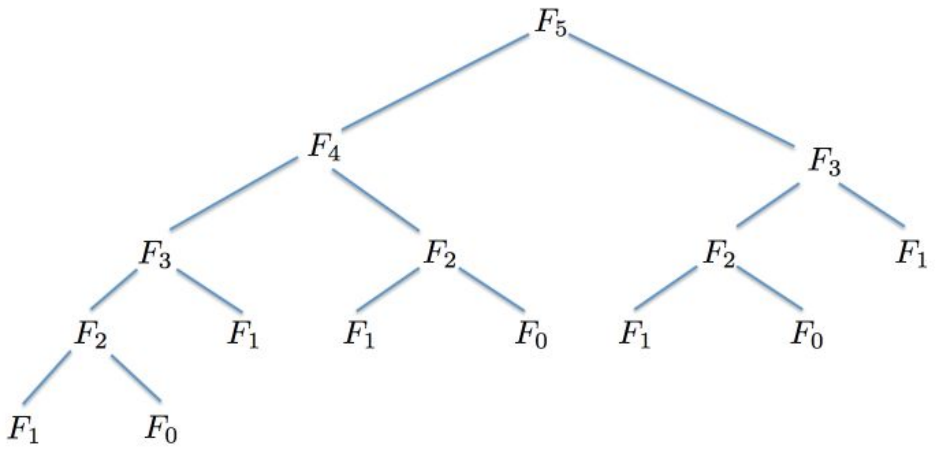
Hemachandra/Fibonacci numbers: 0, 1, 1, 2, 3, 5, 8, 13, 21, 34, 55, 89, 144, ……

$$F_0 := 0;\ F_1 := 1;$$

$$F_n = F_{n-1} + F_{n-2}, \text{ for all } n \geq 2.$$

A trivial algorithm for computing F_n:

```
naive_fib(n):
     if n ≤ 1: return n
     else: return naive_fib(n − 1) +
                    naive_fib(n − 2)
```



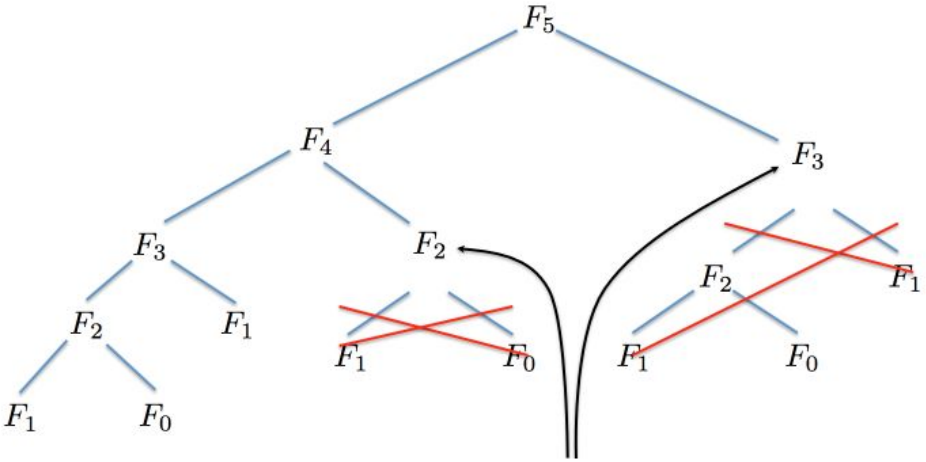
Dynamic programming

Hemachandra/Fibonacci numbers: $F_0 := 0$; $F_1 := 1$; $F_n = F_{n-1} + F_{n-2}$, for all $n \geq 2$.

Never recompute a subproblem $F(k)$, $k \leq n$, if it has been computed before.
Memoization: Remembering previously computed values.

Improved algorithm for computing F_n:

```
memo = { }
fib(n):
    if n in memo: return memo[n]
    else if n = 0: return 0
    else if n = 1: return 1
    else: f = fib(n − 1) + fib(n − 2)
    memo[n] = f
    return f
```



These values are already computed and stored in memo when runtime processes these nodes of the recursion.

Dynamic programming

1. Overlapping Subproblems
2. Optimal Substructure

DP ≈ recursion + memoization (reuse)

- Remember (memoize) previously solved “subproblems”; e.g., in Fibonacci, we memoized the solutions to the subproblems $F_0, F_1, \ldots, F_{n-1}$, while unraveling the recursion.
- If we encounter a subproblem that has already been solved, reuse solution.
- Runtime ≈ (no. of subproblems) * (time per subproblem)

Needleman-Wunsch algorithm

1. Scoring function: substitution matrix & gap penalty
2. Matrix initialization & filling
3. Traceback

Align **GCAT** with **GAT**

Step 1

A scoring scheme:

- Match: 1
- Mismatch: -2
- Gap: -1

	–	G	C	A	T
–					
G					
A					
T					

Needleman-Wunsch algorithm

1. Scoring function: substitution matrix & gap penalty
2. Matrix initialization & filling
3. Traceback

Align **GCAT** with **GAT**

<u>Step 2</u>

```
M(0, j) = j*p
M(i, 0) = i*p

M(i, j) = MAX(   M(i-1, j) + p,          top
                 M(i, j-1) + p,          left
         M(i-1, j-1) + S(A_i, B_j)   )   diagonal
```

	–	G	C	A	T
–					
G					
A					
T					

Needleman-Wunsch algorithm

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```

	–	G	C	A	T
–	0	–1	–2	–3	–4
G	–1				
A	–2				
T	–3				

Needleman-Wunsch algorithm

1. Scoring function: substitution matrix & gap penalty
2. Matrix initialization & filling
3. Traceback

	—	G	C	A	T
—	0	−1	−2	−3	−4
G	−1	?			
A	−2				
T	−3				

	—	G	C	A	T
—	0	−1	−2	−3	−4
G	−1	−2			
A	−2				
T	−3				

	—	G	C	A	T
—	0	−1	−2	−3	−4
G	−1	−2			
A	−2				
T	−3				

	—	G	C	A	T
—	0	−1	−2	−3	−4
G	−1	1			
A	−2				
T	−3				

<u>Step 2</u>

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```

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—	0	−1	−2	−3	−4
G	−1	1			
A	−2				
T	−3				

Needleman-Wunsch algorithm

1. Scoring function: substitution matrix & gap penalty
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Align **GCAT** with **GAT**

<u>Step 2</u>

$$M(0, j) = j*p$$

$$M(i, 0) = i*p$$

$$M(i, j) = \mathrm{MAX}\begin{pmatrix} M(i-1, j) + p, & \text{top} \\ M(i, j-1) + p, & \text{left} \\ M(i-1, j-1) + S(A_i, B_j) & \text{diagonal} \end{pmatrix}$$

	–	G	C	A	T
–	0	−1	−2	−3	−4
G	−1	1	0	−1	−2
A	−2	0	0	1	0
T	−3	−1	−2	0	2

Needleman-Wunsch algorithm

1. Scoring function: substitution matrix & gap penalty
2. Matrix initialization & filling
3. Traceback

$$M(0, j) = j*p$$

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Align **GCAT** with **GAT**

```
GCAT
G-AT
```

Step 3

	–	G	C	A	T
–	0	–1	–2	–3	–4
G	–1	1	0	–1	–2
A	–2	0	0	1	0
T	–3	–1	–2	0	2

Needleman-Wunsch algorithm

1. Scoring function: substitution matrix & gap penalty
2. Matrix initialization & filling
3. Traceback

Align **ATGCT** with **ATTACA**

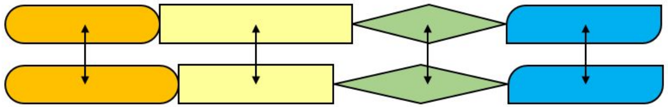
$$M(0, j) = j*p$$
$$M(i, 0) = i*p$$

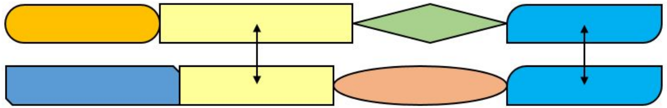
$$M(i, j) = \mathrm{MAX}(\; M(i-1, j) + p, \quad \text{top}$$
$$M(i, j-1) + p, \quad \text{left}$$
$$M(i-1, j-1) + S(A_i, B_j) \;) \quad \text{diagonal}$$

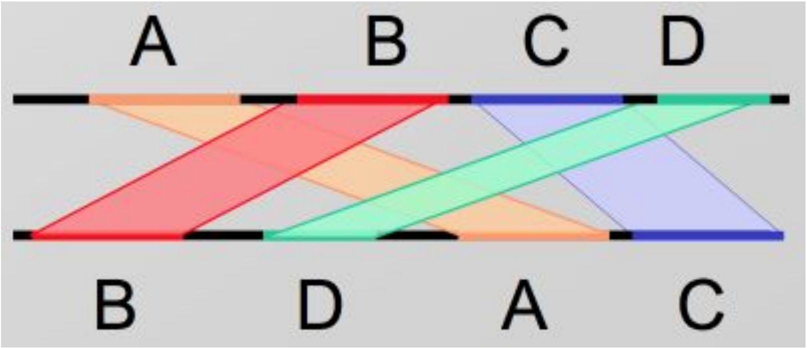
	-	A	T	T	A	C	A
-							
A							
T							
G							
C							
T							

Global & local alignment

A local alignment of strings s and t is an alignment of a substring of s with a substring of t.


Global Alignment


Local Alignment



Smith-Waterman algorithm

Similar to Needleman-Wunsch, with 3 changes:

- First row/column set to 0.
- No negative scores, set to 0.
- Backtrack from cell with highest score, stop at 0.

Align **GCAT** with **GCT**

```
M(0, j) = 0
M(i, 0) = 0

M(i, j) = MAX(                0,
                 M(i-1, j) + p,        top
                 M(i, j-1) + p,        left
          M(i-1, j-1) + S(A_i, B_j)  )  diagonal
```

	–	G	C	A	T
–					
G					
C					
T					

Smith-Waterman algorithm

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                 M(i-1, j) + p,        top
                 M(i, j-1) + p,        left
          M(i-1, j-1) + S(Ai, Bj)   )  diagonal
```

Align **GCAT** with **GCT**

GC
GC

	–	G	C	A	T
–	0	0	0	0	0
G	0	1	0	0	0
C	0	0	2	1	0
T	0	0	1	1	2