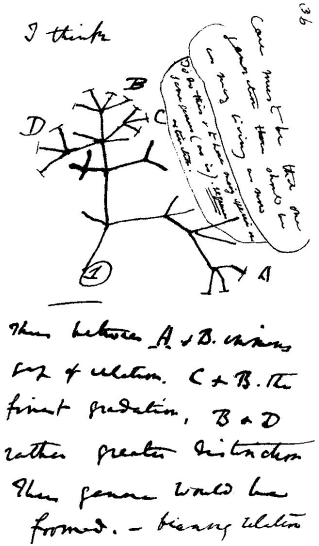
Week 2: Sequence alignment & search

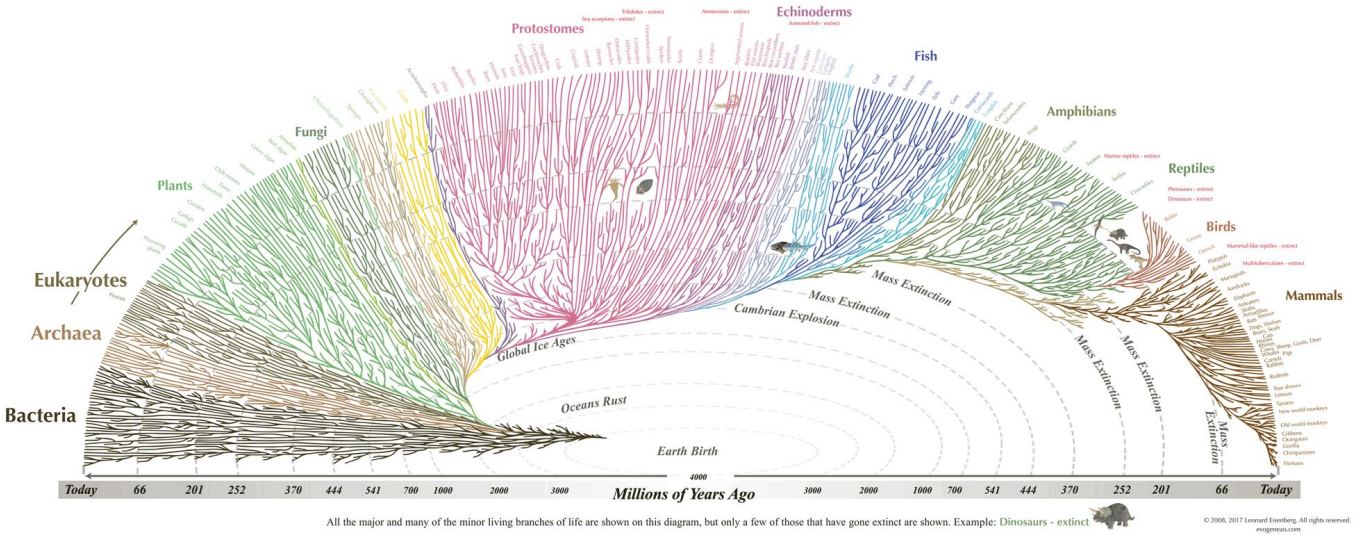
Alignment

- Sequence alignment problem
- Dynamic programming
- Global alignment
  - Needleman-Wunsch algorithm
- Local alignment
  - Smith-Waterman algorithm

- Sign into Pear Deck using the link on Slack
  - Keep a paper and a pen(cil) ready

Sequence evolution

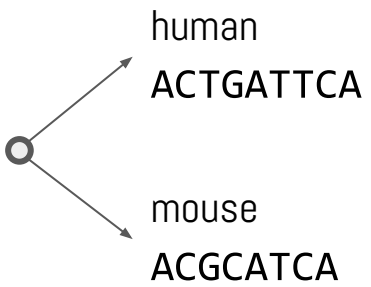




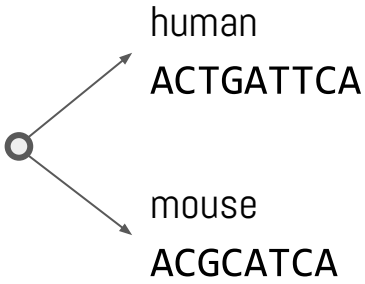
deletion mutation insertion

ACATGGTCA → AC*TGGTCA → ACTGATCA → ACTGATTCA

Evolutionary time



Sequence alignment



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

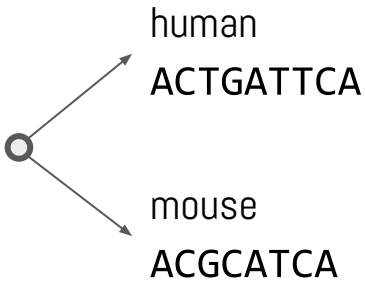
```
ACTGATTCA
ACGCA-TCA
```

```
ACTGATTCA
AC-GCATCA
```

```
ACTG-ATTCA
AC-GCAT-CA
```

Which alignment is correct?

Sequence alignment



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 **subproblems** 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

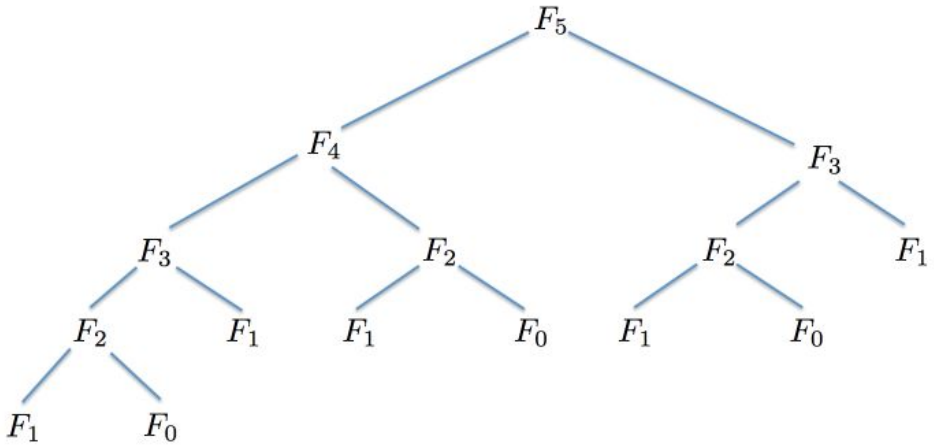
Hemachandra/Fibonacci numbers: 0, 1, 1, 2, 3, 5, 8, 13, 21, 34, 55, 89, 144, ...

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

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

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)
```



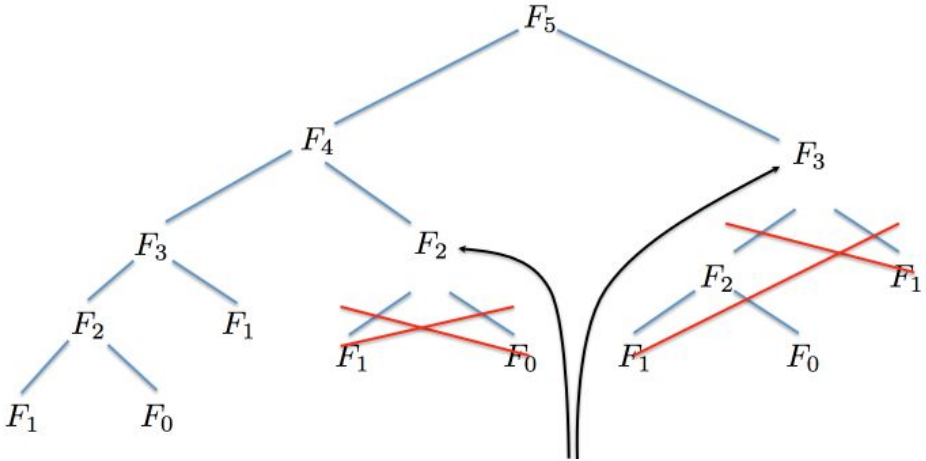
Dynamic programming

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 $F_0, F_1, \cdots, F_{n-1}$, 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
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3. Traceback

A scoring scheme:
- Match: **1**
- Mismatch: **−2**
- Gap: **−1**

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

p: gap penalty
$s(S1_i, S2_j)$: match/mismatch score

Step 2

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

$$M(i, j) = MAX(\ M(i-1, j) + p,\ M(i, j-1) + p,\ M(i-1, j-1) + s(S1_i, S2_j))$$

top
left
diagonal

	—	G	C	A	T
—					
G					
A					
T					

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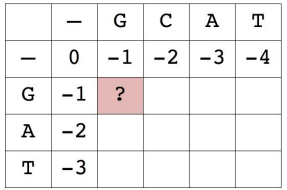
top
left
diagonal

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

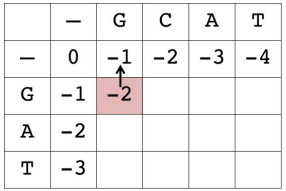
Needleman-Wunsch algorithm

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

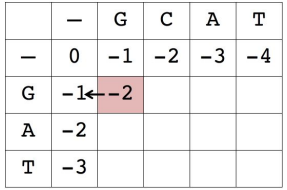
A scoring scheme:
- Match: **1**
- Mismatch: **−2**
- Gap: **−1**



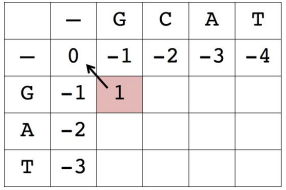
	—	G	C	A	T
—	0	−1	−2	−3	−4
G	−1	?			
A	−2				
T	−3				



	—	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				

p: gap penalty
$s(S1_i, S2_j)$: match/mismatch score

Step 2

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

$$M(i, j) = \mathrm{MAX}(\ M(i-1, j) + p,\ M(i, j-1) + p,\ M(i-1, j-1) + s(S1_i, S2_j))$$

top

left

diagonal

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

Needleman-Wunsch algorithm

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

A scoring scheme:
- Match: **1**
- Mismatch: **−2**
- Gap: **−1**

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

Fill the remaining cells in this matrix.

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

Step 2

p: gap penalty
$s(S1_i, S2_j)$: match/mismatch score

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

$$M(i, j) = MAX(\ M(i-1, j) + p,\ \text{top}$$
$$M(i, j-1) + p,\ \text{left}$$
$$M(i-1, j-1) + s(S1_i, S2_j))\ \text{diagonal}$$

Needleman-Wunsch algorithm

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

A scoring scheme:
- Match: **1**
- Mismatch: **−2**
- Gap: **−1**

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

p: gap penalty
$s(S1_i, S2_j)$: match/mismatch score

Step 2

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

$$M(i, j) = \mathrm{MAX}\begin{cases} M(i-1, j) + p, & \text{top} \\ M(i, j-1) + p, & \text{left} \\ M(i-1, j-1) + s(S1_i, S2_j) & \text{diagonal} \end{cases}$$

	—	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

A scoring scheme:
- Match: **1**
- Mismatch: **−2**
- Gap: **−1**

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

p: gap penalty
$s(S1_i, S2_j)$: match/mismatch score

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

$$M(i, j) = MAX(\ M(i-1, j) + p,\ M(i, j-1) + p,\ M(i-1, j-1) + s(S1_i, S2_j))$$

top
left
diagonal

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

A scoring scheme:
- Match: **1**
- Mismatch: **−2**
- Gap: **−1**

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

What is the alignment?

p: gap penalty
$s(S1_i, S2_j)$: match/mismatch score

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

$$M(i, j) = \mathrm{MAX}(\ M(i-1, j) + p,\ \text{top}$$
$$M(i, j-1) + p,\ \text{left}$$
$$M(i-1, j-1) + s(S1_i, S2_j)) \ \text{diagonal}$$

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

A scoring scheme:
- Match: **1**
- Mismatch: **−2**
- Gap: **−1**

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

```
GCAT
G-AT
```

```
p: gap penalty
s(S1_i, S2_j): match/mismatch score

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(S1_i, S2_j))   diagonal
```

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

A scoring scheme:
- Match: **1**
- Mismatch: **−2**
- Gap: **−1**

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

p: gap penalty
$s(S1_i, S2_j)$: match/mismatch score

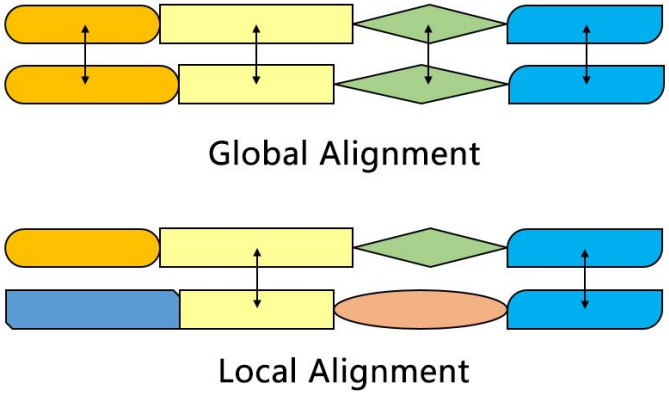
$$M(0, j) = j*p;\ M(i, 0) = i*p$$

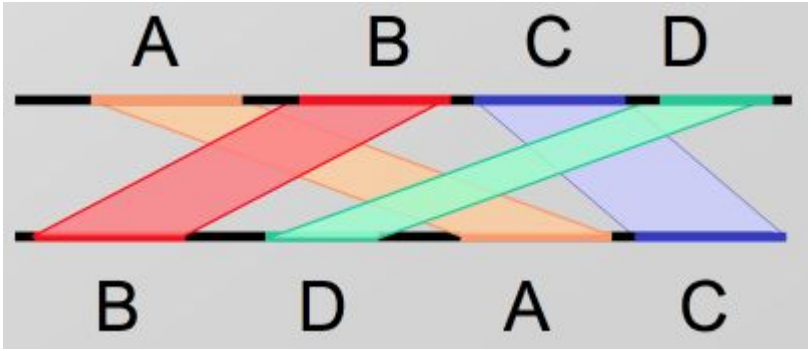
$$M(i, j) = MAX(\ M(i-1, j) + p,\ \text{top}$$
$$M(i, j-1) + p,\ \text{left}$$
$$M(i-1, j-1) + s(S1_i, S2_j))\ \text{diagonal}$$

	−	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*.





Smith-Waterman algorithm

Similar to Needleman-Wunsch, with 3 changes:

- First row/column set to 0.
- No negative scores; set to 0. (Don't record direction.)
- Backtrack from cell with highest score & stop at 0.

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

What are the values in the first row and first column?

	–	G	C	A	T
–					
G					
C					
T					

p: gap penalty
$s(S1_i, S2_j)$: match/mismatch score

$$M(0, j) = 0;\ M(i, 0) = 0$$

$$M(i, j) = MAX(\ 0,$$

$$M(i-1, j) + p,$$ top

$$M(i, j-1) + p,$$ left

$$M(i-1, j-1) + s(S1_i, S2_j))$$ diagonal

Smith-Waterman algorithm

Similar to Needleman-Wunsch, with 3 changes:

- First row/column set to 0.
- No negative scores; set to 0. (Don't record direction.)
- Backtrack from cell with highest score & stop at 0.

p: gap penalty
$s(S1_i, S2_j)$: match/mismatch score

$$M(0, j) = 0;\ M(i, 0) = 0$$

$$M(i, j) = MAX(\ 0,$$

$$M(i-1, j) + p,$$ top

$$M(i, j-1) + p,$$ left

$$M(i-1, j-1) + s(S1_i, S2_j))$$ diagonal

Align GCAT with GCT

Fill this matrix and
enter the highest value.

	-	G	C	A	T
-					
G					
C					
T					

Smith-Waterman algorithm

Similar to Needleman-Wunsch, with 3 changes:

- First row/column set to 0.
- No negative scores; set to 0. (Don't record direction.)
- Backtrack from cell with highest score & stop at 0.

Align GCAT with GCT

GC
GC

p: gap penalty
$s(S1_i, S2_j)$: match/mismatch score

$$M(0, j) = 0;\ M(i, 0) = 0$$

$$M(i, j) = MAX(\ 0,$$

$$M(i-1, j) + p,$$ top

$$M(i, j-1) + p,$$ left

$$M(i-1, j-1) + s(S1_i, S2_j))$$ diagonal

	-	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