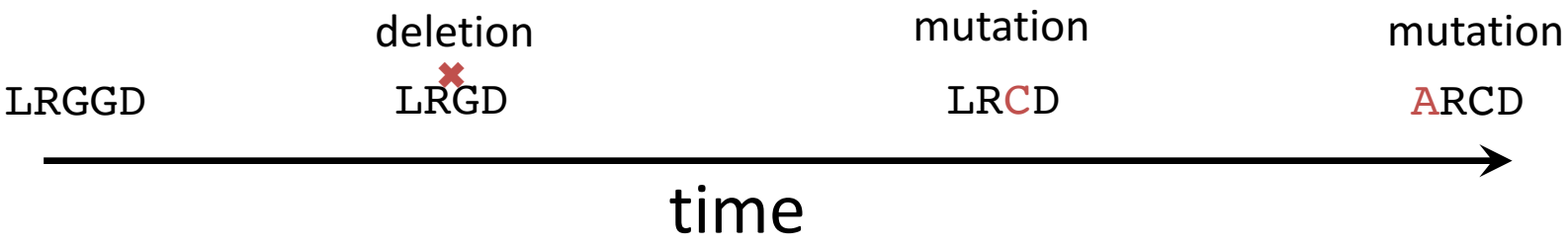
Sequence alignments

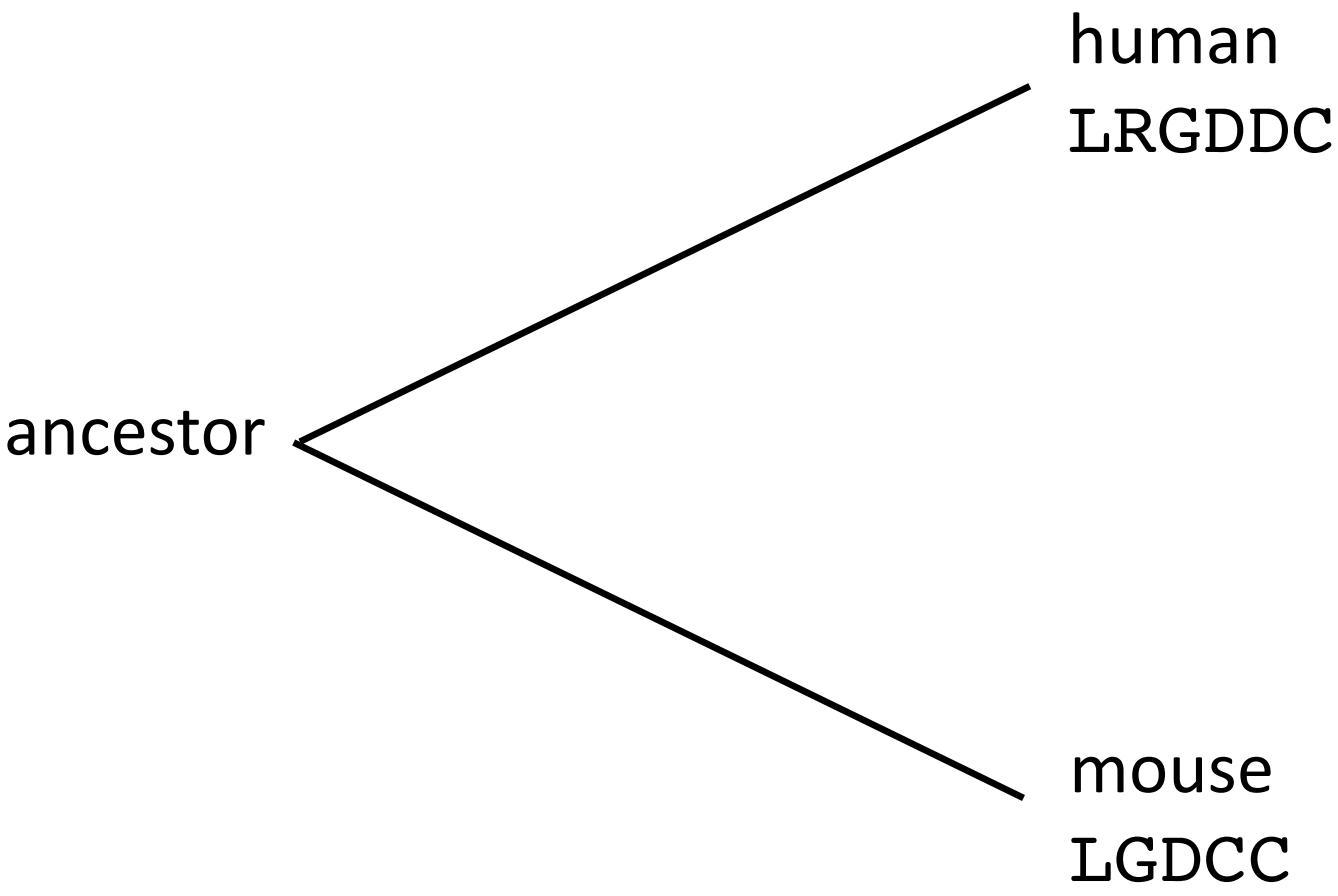
Genetic sequences change over time



Relationship between original and final sequence:

```
LRGGD      or    LRGGD
AR-CD            ARC-D
```

In practice: we only know sequences from extant organisms



We need to align these sequences to compare them

human
LRGDDC

mouse
LGDCC

```
LRGDDC
L-GDCC
```

```
LRGDDC-
L-GD-CC
```

```
LRGDDC
-LGDCC
```

Which alignment is correct?

We need to score the alignment

Example:

- match = +1
- mismatch = -1
- gap = 0

```
LRGDDC      score = 1+0+1+1-1+1
L-GDCC            = 3
```

```
LRGDDC-     score = 1+0+1+1+0+1+0
L-GD-CC           = 4
```

```
LRGDDC      score = 0-1+1+1-1+1
-LGDCC            = 1
```

We need to score the alignment

Example:

- match = +1
- mismatch = -1
- gap = -2

```
LRGDDC      score = 1-2+1+1-1+1
L-GDCC            = 1
```

```
LRGDDC-     score = 1-2+1+1-2+1-2
L-GD-CC           = -2
```

```
LRGDDC      score = -2-1+1+1-1+1
-LGDCC            = -1
```

We often score by amino-acid similarity

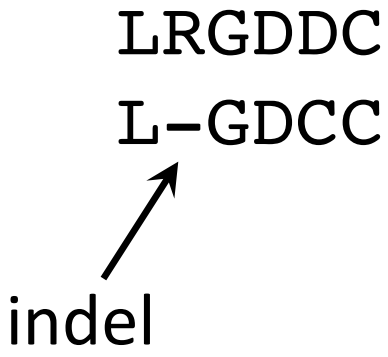
	Ala	Arg	Asn	Asp	Cys	Gln	Glu	Gly	His	Ile	Leu	Lys	Met	Phe	Pro	Ser	Thr	Trp	Tyr	Val
Ala	4																			
Arg	-1	5																		
Asn	-2	0	6																	
Asp	-2	-2	1	6																
Cys	0	-3	-3	-3	9															
Gln	-1	1	0	0	-3	5														
Glu	-1	0	0	2	-4	2	5													
Gly	0	-2	0	-1	-3	-2	-2	6												
His	-2	0	1	-1	-3	0	0	-2	8											
Ile	-1	-3	-3	-3	-1	-3	-3	-4	-3	4										
Leu	-1	-2	-3	-4	-1	-2	-3	-4	-3	2	4									
Lys	-1	2	0	-1	-3	1	1	-2	-1	-3	-2	5								
Met	-1	-1	-2	-3	-1	0	-2	-3	-2	1	2	-1	5							
Phe	-2	-3	-3	-3	-2	-3	-3	-3	-1	0	0	-3	0	6						
Pro	-1	-2	-2	-1	-3	-1	-1	-2	-2	-3	-3	-1	-2	-4	7					
Ser	1	-1	1	0	-1	0	0	0	-1	-2	-2	0	-1	-2	-1	4				
Thr	0	-1	0	-1	-1	-1	-1	-2	-2	-1	-1	-1	-1	-2	-1	1	5			
Trp	-3	-3	-4	-4	-2	-2	-3	-2	-2	-3	-2	-3	-1	1	-4	-3	-2	11		
Tyr	-2	-2	-2	-3	-2	-1	-2	-3	2	-1	-1	-2	-1	3	-3	-2	-2	2	7	
Val	0	-3	-3	-3	-1	-2	-2	-3	-3	3	1	-2	1	-1	-2	-2	0	-3	-1	4

BLOSUM62 Matrix

$$score = \log \frac{p_{ij}}{p_i p_j}$$

http://commons.wikimedia.org/wiki/File:BLOSUM62.gif

Gaps in alignments are called “indels”



Can you guess why?

How do we find the best alignment given a scoring system?

Global alignment: Needleman-Wunsch algorithm

Example: align GCAT and GAT

Scoring: match = 1, mismatch = -1, gap = -1

	-	G	C	A	T
-					
G					
A					
T					

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Scoring: match = 1, mismatch = -1, gap = -1

	–	G	C	A	T
–	0				
G					
A					
T					

Alignment:

–

–

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Example: align GCAT and GAT

Scoring: match = 1, mismatch = -1, gap = -1

	–	G	C	A	T
–	0	-1			
G					
A					
T					

Alignment:

–G

–-

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Example: align GCAT and GAT

Scoring: match = 1, mismatch = -1, gap = -1

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

Alignment:

–GC

–––

How do we find the best alignment given a scoring system?

Global alignment: Needleman-Wunsch algorithm

Example: align GCAT and GAT

Scoring: match = 1, mismatch = -1, gap = -1

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

Alignment:

–GCAT

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Example: align GCAT and GAT

Scoring: match = 1, mismatch = -1, gap = -1

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

Alignment:

––

–G

How do we find the best alignment given a scoring system?

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Example: align GCAT and GAT

Scoring: match = 1, mismatch = -1, gap = -1

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

Alignment:

```
----
-GAT
```

How do we find the best alignment given a scoring system?

Global alignment: Needleman-Wunsch algorithm

Example: align GCAT and GAT

Scoring: match = 1, mismatch = -1, gap = -1

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

How do we find the best alignment given a scoring system?

Global alignment: Needleman-Wunsch algorithm

Example: align GCAT and GAT

Scoring: match = 1, mismatch = -1, gap = -1

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

Alignment:

–G–

––G

How do we find the best alignment given a scoring system?

Global alignment: Needleman-Wunsch algorithm

Example: align GCAT and GAT

Scoring: match = 1, mismatch = -1, gap = -1

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

Alignment:

––G

–G–

How do we find the best alignment given a scoring system?

Global alignment: Needleman-Wunsch algorithm

Example: align GCAT and GAT

Scoring: match = 1, mismatch = -1, gap = -1

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

Alignment:

–G

–G

How do we find the best alignment given a scoring system?

Global alignment: Needleman-Wunsch algorithm

Example: align GCAT and GAT

Scoring: match = 1, mismatch = -1, gap = -1

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

Alignment:

–GC

–G–

How do we find the best alignment given a scoring system?

Global alignment: Needleman-Wunsch algorithm

Example: align GCAT and GAT

Scoring: match = 1, mismatch = -1, gap = -1

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

Alignment:

–G–

–GA

How do we find the best alignment given a scoring system?

Global alignment: Needleman-Wunsch algorithm

Example: align GCAT and GAT

Scoring: match = 1, mismatch = -1, gap = -1

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

Alignment:

–GC–

–G–A

How do we find the best alignment given a scoring system?

Global alignment: Needleman-Wunsch algorithm

Example: align GCAT and GAT

Scoring: match = 1, mismatch = -1, gap = -1

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

Alignment:

–G–C

–GA–

How do we find the best alignment given a scoring system?

Global alignment: Needleman-Wunsch algorithm

Example: align GCAT and GAT

Scoring: match = 1, mismatch = -1, gap = -1

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

Alignment:

–GC

–GA

How do we find the best alignment given a scoring system?

Global alignment: Needleman-Wunsch algorithm

Example: align GCAT and GAT

Scoring: match = 1, mismatch = -1, gap = -1

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

How do we find the best alignment given a scoring system?

Global alignment: Needleman-Wunsch algorithm

Example: align GCAT and GAT

Scoring: match = 1, mismatch = -1, gap = -1

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

Alignment:

–GCAT

–G–AT

Needleman-Wunsch algorithm, mathematical form

$$\mathbf{M}(0, j) = j \times p$$ first row, p = gap penalty

$$\mathbf{M}(i, 0) = i \times p$$ first column

$$\mathbf{M}(i, j) = \max \begin{pmatrix} \mathbf{M}(i-1, j) + p \\ \mathbf{M}(i, j-1) + p \\ \mathbf{M}(i-1, j-1) + s(a_j, b_i) \end{pmatrix}$$ top / left / diagonal

$s(a_j, b_i)$ = match/mismatch score for sites j and i in sequences a and b

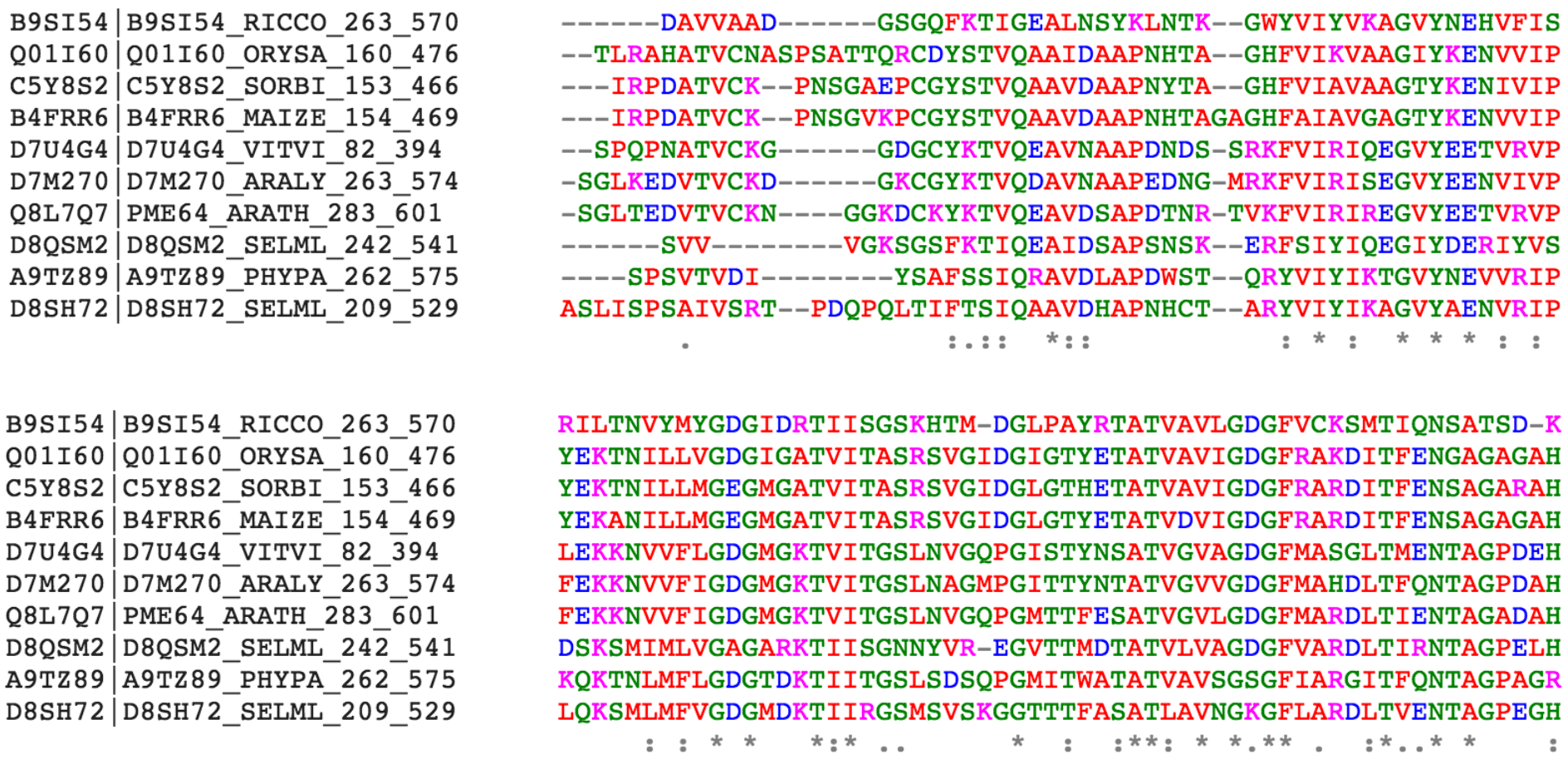
Now try on your own

Align `ATGCT` and `ATTACA`

Scoring: match = 1, mismatch = -1, gap = -1

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

Multiple sequence alignment (MSA)



Software to generate MSAs

- MAFFT
  (very good, very fast)
  http://mafft.cbrc.jp/alignment/software/
- Clustal Omega
  (very good, very fast)
  http://www.ebi.ac.uk/Tools/msa/clustalo/
- PRANK
  (extremely good, very slow)
  http://wasabiapp.org/software/prank/