Inexact matching, sequence alignment and dynamic programming

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Edit distance, alignment and dynamic programming

Overview

- Reflection on string matching and string similarity
- Edit distance
- Recursive calculation of edit distance
- Dynamic programming and calculation of edit distance

Exact vs inexact matching

- Up until now we were referring to exact matching
  - Good for sequence search problems but not for sequence comparison
- Effect of sequencing error and mutational processes
- Approximate matching: certain errors are acceptable in valid matches

Exact vs inexact matching

- **Alignment:** lining up characters of strings, allowing mismatches as well as matches, and allowing characters of one string to be placed opposite spaces made in opposing string.
- Usage:
  - Difference between two strings, string similarity
  - String alignment
    - Global alignment (end-to-end alignment)
    - Local alignment

Exact vs inexact matching

- Substring vs subsequence
  - Substring: contiguous
  - Subsequence: doesn’t have to be contiguous

Example:

- String: a**x**a**y**a**z**
- Subsequence: xyz - not a substring

First fact of biological sequence analysis

In biomolecular sequence (DNA, RNA or amino acid sequences) high sequence similarity usually implies significant functional or structural similarity.
(**Note:** opposite not necessarily true)

Evolution**:**

- Reuses, builds on and modifies “successful” structures
- Duplication with modification - central paradigm of protein evolution

Importance of (sub)sequence comparison in Molecular Biology

Redundancy:

- "...built in characteristics of protein sequences"
- New sequences resemble already known sequences (between species)

Example:

- Same genes that work in flies are the ones that work in humans
- "...studies on yeast are remarkable predictors of the human system"

Consequence: **sequence similarity (redundancy) implies functional similarity**

- Helps us to infer *conserved* features
- Large-scale sequence comparison (database search) is a very powerful tool in biological inference in molecular biology

Measure for sequence similarity (distance)

If we could measure distance between two strings we could quantify similarity between organisms

Need for measure of difference or *distance* between two strings (**distance function** or **metrics**)

- Spelling correction, evolutionary studies of biological strings…

Hamming distance

Number of single letter substitutions needed from S to T.

```
ACTGACTGACTG
|  |  |  |  |     |  |       |  |
ACTGAGTGTTTG
```

Hamming distance of 3

Hamming distance - not so great

- Works only on strings of the same length
- Does not properly reflect mutational processes occurring in the genome
- For strings of the same length:
  - editDistance(x,y)$\leq$hammingDistance(x,y)
- If they are not:
  - editDistance(x,y)$\geq$||x|-|y||

```
GAGGTAGCGGCGTTTAAC
|  |||||  |||  |||||||
GTGGTAACGGGGTTTAAC
```

Hamming distance

```
GCGTATGCGGCTA-ACGC
||  |||||||||||  |||
GC-TATGCGGCTATACGC
```

Edit distance

Edit distance (Levenshtein distance)

Edit distance: focuses on editing(transforming) one string into the other by a series of edit operations on individual characters.

Which operations?

Edit distance - edit operations

A *mismatch* is a single-character substitution:

```
X:  G T A G C G G C G
    | | |   | | | | |
Y:  G T A A C G G C G
```

denoted R - replacement(substitution)

An *edit* is a single-character substitution or gap (*insertion* or *deletion*):

```
X:  G T A G C G G C G
    | | |   | | | | |
Y:  G T A A C G G C G

                Gap in X
X:  G T A G C - G C G
    | | | | |   | | |
Y:  G T A G C G G C G

X:  G T A G C G G C G
    | |   | | | | | |
Y:  G T - G C G G C G
Gap in Y
```

AKA insertion in Y or deletion in X

AKA insertion in X or deletion in Y

And M for *match* or nonoperation...

Alignment

This is an alignment: way of lining up characters of x and y.

```
GAGGTAGCGGCGTTTAAC
|  |||||  |||  |||||||
GTGGTAACGGGGTTTAAC
```

Alignment: lining up characters of strings, allowing mismatches as well as matches, and allowing characters of one string to be placed opposite spaces made in opposing string.

Edit distance - an example

Transforming “vintner” into “writers”

RIMDMDMMI

```
v intner
  | |  | |
wri t ers
```

Edit distance and edit transcript

Can think of edits as being introduced by an optimal editor working left-to-right.

Edit transcript describes how editor turns x into y.

```
x: GCGTATGCGGCTAACGC
y: GCTATGCGGCTATACGC
```

```
x: GCGTATGCGGCTAACGC
   | |
y: GC-TATGCGGCTATACGC
```

MMD

```
x: GCGTATGCGGCTA-ACGC
   | |  | | | | | | | | |
y: GC- TATGCGGCTATACGC
```

MMDMMMMMMMMMMI

```
x: GCGTATGCGGCTA-ACGC
   | |  | | | | | | | | |  | | | |
y: GC- TATGCGGCTATACGC
```

MMDMMMMMMMMMMIMMMM

Operations:

M = match, R = replace,

I = insert into *x*, D = delete from *x*

Edit distance and edit transcript

Edit transcript: A string over alphabet D, R, M, I that describes a transformation of one string to another is called an *edit transcript*, or transcript for short, of two strings.

Edit distance: Edit distance between two strings is defined as a minimum number of edit operations - insertions, deletions and substitutions - needed to transform first string into second. **Note:** matches are not counted.

Optimal transcript: Edit transcript that uses minimal number of edit operations. (note: there may be more than one optimal edit transcripts, *cooptimal transcripts*)

Edit distance and edit transcript

Alignments:

Edit transcripts with respect to *x*:

```
x: GCGTATGCGGCTA-ACGC
   | |  |||| |||||||  ||||
y: GC- TATGCGGCTATACGC
```

MMDMMMMMMMMMMMIMMMM

Distance = 2

```
x: GCGTATGAGGCTA-ACGC
   | |  |||| |  || ||| |||| |
y: GC- TATGCGGCTATACGC
```

MMDMMMMRMMMMMIMMMM

Distance = 3

```
x: the longest----
       |||||||
y: ----longest day
```

DDDDMMMMMMMMIIII

Distance = 8

Edit distance problem

Edit distance problem: compute edit distance between two strings with an optimal edit transcript that describes the transformation.

Important note: edit distance is defined as a number of operation on first string needed to transform it into the second string.

But!: it's also sometimes though as the minimum number of operations done on either of two strings to transform them into the common third string. This is ok.
Why?: Insertion in one string can be viewed as deletion in another.

Digression: more on alignment

(Global) alignment of two strings S1 and S2 is obtained by first inserting chosen spaces (or dashes) either into (or at the end of) S1 or S2 and then placing one resulting string above the other so that so that every character (or space) in one string is opposite a unique character (or space) in another string.

- An alternative way (to edit transcript) to represent transformation of one string to another

```
v_intner_
wri_t_ers
```

Alignment vs edit transcript

- **Mathematically they are equivalent** ways in describing the relations between two strings
- Can be converted from one to another easily
  - Example: vintner, writer
- Edit distance is given by the alignment minimizing the number of opposing characters that mismatch plus the number of characters opposite spaces.

Alignment vs edit transcript

- **Not equivalent** from modelling perspective

Edit transcript	**vs**	**Alignment**
Mutational events		Relationships between the two strings
<u>Process</u>	vs	<u>Product</u>

- Alignment alone blurs mutational model
  - Different evolutionary models have different edit operations which can result with same alignments

Dynamic programming

Dynamic programming is a method for solving a complex problem by breaking it down into a collection of simpler subproblems, solving each of those subproblems just once, and storing their solutions.

The technique of storing solutions to subproblems instead of recomputing them is called "memoization".

Dynamic programming

"For many optimization problems, the following principle of optimality holds: **an optimal solution is composed of optimal solutions to subproblems**. If a subproblem has several optimal solutions, it does not matter which one is used.

The idea of dynamic programming is to build an exhaustive table of optimal solutions. We start with trivial subproblems. We build optimal solutions for increasingly larger problems by constructing them from tabulated solutions of smaller problems."

K. Mehlhorn, P. Sanders(2010): "Algorithms and Data structures", Springer

Dynamic programming organizes computations to avoid re-computing values that you already know, which can often save a great deal of time.

N.C.Jones, P. Pevzner, P. Sanders(2004): "An Introduction to Bioinformatics Algorithms", MIT Press

Dynamic programming and calculation of edit distance

Dynamic programming is a method for solving a complex problem by breaking it down into a collection of simpler subproblems, solving each of those subproblems just once, and storing their solutions.

If len(S1)=n and len(S2)=m, we compute D(n,m) by computing D(i,j) for all i,j combinations where $i \in [1,n]$ and $j \in [1,m]$.

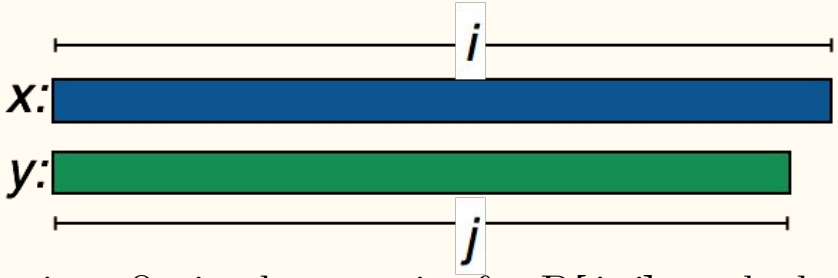
Dynamic programming (in our case) has three components:

1. Recurrence relation
2. Tabular (bottom-up) computation
3. Traceback

Dynamic programming and calculation of edit distance

Def: D(i, j) denotes the minimum number of edit operations needed to transform the first i characters of S1 into the first j characters of S2.

D[i, j]: edit distance between length-i prefix of S1 (S1[1...i]) and length-j prefix of S2 (S2[1...j]).



Think in terms of edit transcript. Optimal transcript for D[i, j] can be built by extending a shorter one by 1 operation. Only 3 options:

- Append D to transcript for D[i-1, j]
- Append I to transcript for D[i, j-1]
- Append M or R to transcript for D[i-1, j-1]

D[i, j] is minimum of the three, and D[$|x|$, $|y|$] is the overall edit distance

Recurrence relation

Base conditions:

$$\mathbf{D(i,0)=i}$$

$$\mathbf{D(0,j)=j}$$

and recurrence relation ($i > 0$, $j > 0$):

D I R or M

$$\mathbf{D(i,j)=min\ [D(i\text{-}1,j)+1,\ D(i,\ j\text{-}1)+1,\ D(i\text{-}1,j\text{-}1)+\delta(i,j)]}, \text{ where}$$

$\boldsymbol{\delta}$**(i,j)=1 if S1[i-1]≠S2[j-1]** (R) else **if S1[i-1]=S2[j-1],** $\boldsymbol{\delta}$**(i,j)=0** (M).

Recurrence relation

We can easily implement it as a recursion (see notebook and play a bit with it).

Issue? -> Running time

```
>>> import datetime as d
>>> st = d.datetime.now(); \
... edDistRecursive("Shakespeare", "shake spear"); \
... print (d.datetime.now()-st).total_seconds()
3
31.498284
```

Because we have (n+1)x(m+1) potential recursive calls.

Recurrence relation

Solution: memoization

Remember memoize when we once calculate certain D(i,j), then reuse it if the need appears (code in the notebook).

```
>>> import datetime as d
>>> st = d.datetime.now(); \
... edDistRecursiveMemo("Shakespeare", "shake spear"); \
... print (d.datetime.now()-st).total_seconds()
3
0.000593
```

Recurrence relation

But!

For large strings, it would still take a lot of time (remember, we are talking about genome-scale data).

Recursive approach is **top-down** approach.

How about **bottom-up** approach?

Tabular (bottom-up) computation

ϵ is empty string

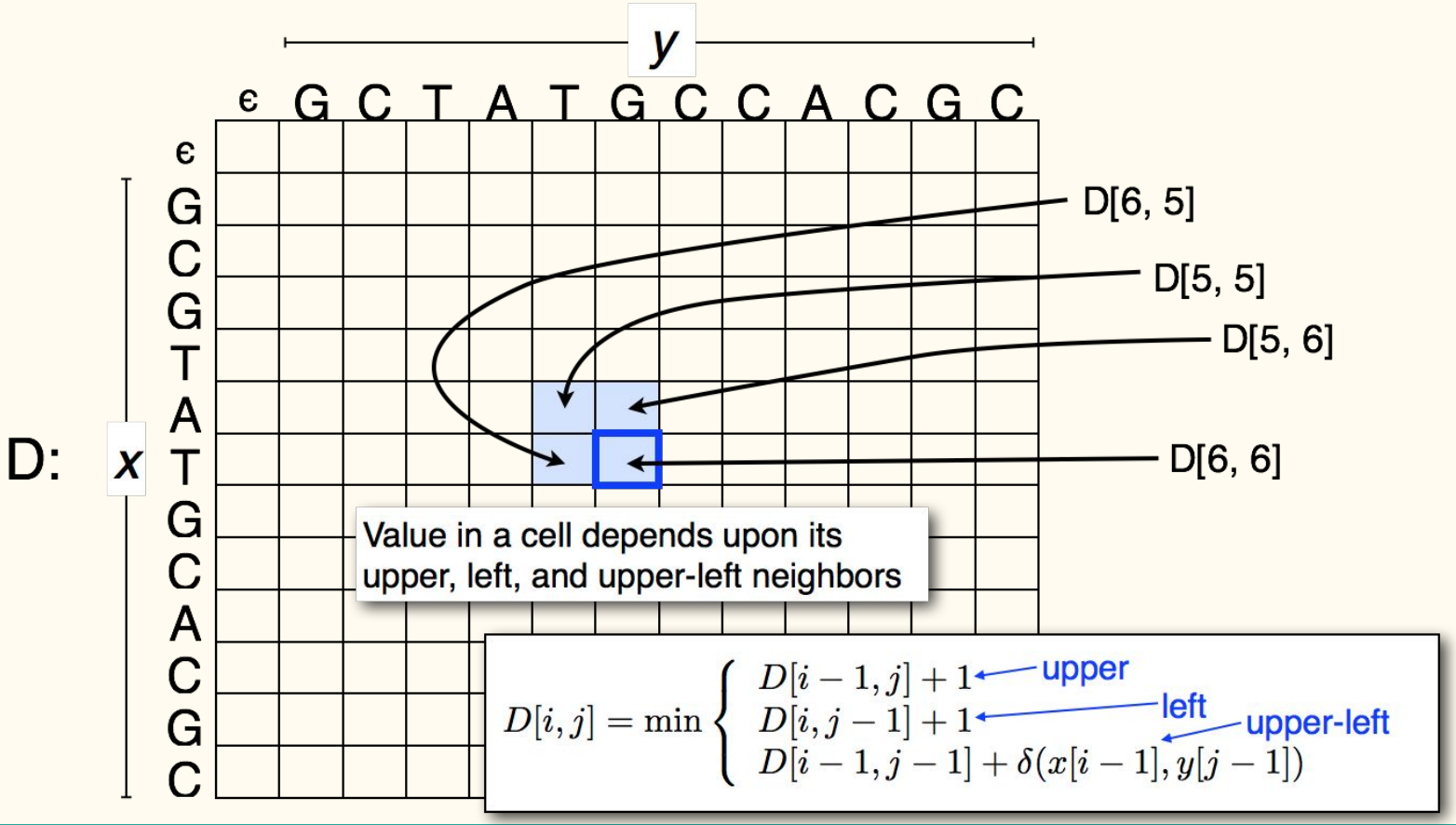
D: x \ y	ϵ	G	C	T	A	T	G	C	C	A	C	G	C
ϵ													
G													
C													
G													
T													
A													
T													
G													
C													
A													
C													
G													
C													

Let $n = |x|$, $m = |y|$

D: $(n+1) \times (m+1)$ matrix

D[i, j] = edit distance b/t length-i prefix of x and length-j prefix of y

Tabular (bottom up) computation - recurrence relation



Tabular (bottom up) computation - table initialization

	ϵ	G	C	T	A	T	G	C	C	A	C	G	C
ϵ	0	1	2	3	4	5	6	7	8	9	10	11	12
G	1												
C	2												
G	3												
T	4												
A	5												
T	6												
G	7												
C	8												
A	9												
C	10												
G	11												
C	12												

Initialize D[0, *j*] to *j*,
D[*i*, 0] to *i*

Tabular (bottom up) computation - filling up the table

	ϵ	G	C	T	A	T	G	C	C	A	C	G	C
ϵ	0	1	2	3	4	5	6	7	8	9	10	11	12
G	1												
C	2												
G	3												
T	4												
A	5						etc						
T	6												
G	7												
C	8												
A	9												
C	10												
G	11												
C	12												

Fill remaining cells from top row to bottom and from left to right

Tabular (bottom up) computation

	ϵ	G	C	T	A	T	G	C	C	A	C	G	C
ϵ	0	1	2	3	4	5	6	7	8	9	10	11	12
G	1	?											
C	2												
G	3												
T	4												
A	5												
T	6												
G	7												
C	8												
A	9												
C	10												
G	11												
C	12												

Fill remaining cells from top row to bottom and from left to right

What goes here in **i=1,j=1**?

x[i-1] = y[j-1] = 'G ',

SO delt = 0

```
D[i, j] = min(D[i-1, j-1]+delt,
              D[i-1, j]+1,
              D[i, j-1]+1)
        = min(0 + 0, 1 + 1, 1 + 1)
        = 0
```

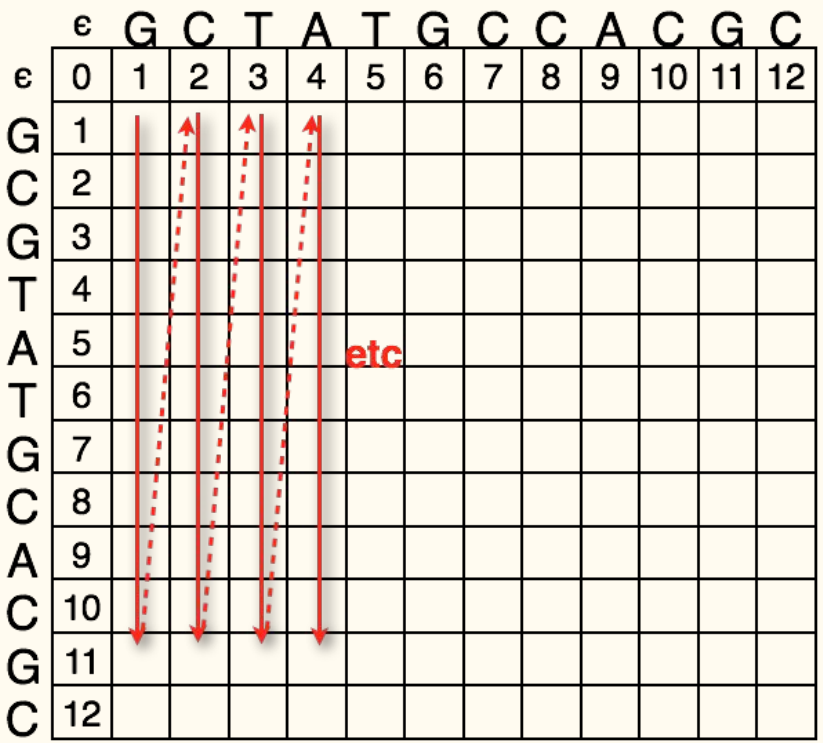
Fast forward...

	ϵ	G	C	T	A	T	G	C	C	A	C	G	C
ϵ	0	1	2	3	4	5	6	7	8	9	10	11	12
G	1	0	1	2	3	4	5	6	7	8	9	10	11
C	2	1	0	1	2	3	4	5	6	7	8	9	10
G	3	2	1	1	2	3	3	4	5	6	7	8	9
T	4	3	2	1	2	2	3	4	5	6	7	8	9
A	5	4	3	2	1	2	3	4	5	5	6	7	8
T	6	5	4	3	2	1	2	3	4	5	6	7	8
G	7	6	5	4	3	2	1	2	3	4	5	6	7
C	8	7	6	5	4	3	2	1	2	3	4	5	6
A	9	8	7	6	5	4	3	2	2	2	3	4	5
C	10	9	8	7	6	5	4	3	2	3	2	3	4
G	11	10	9	8	7	6	5	4	3	3	3	2	3
C	12	11	10	9	8	7	6	5	4	4	3	3	2

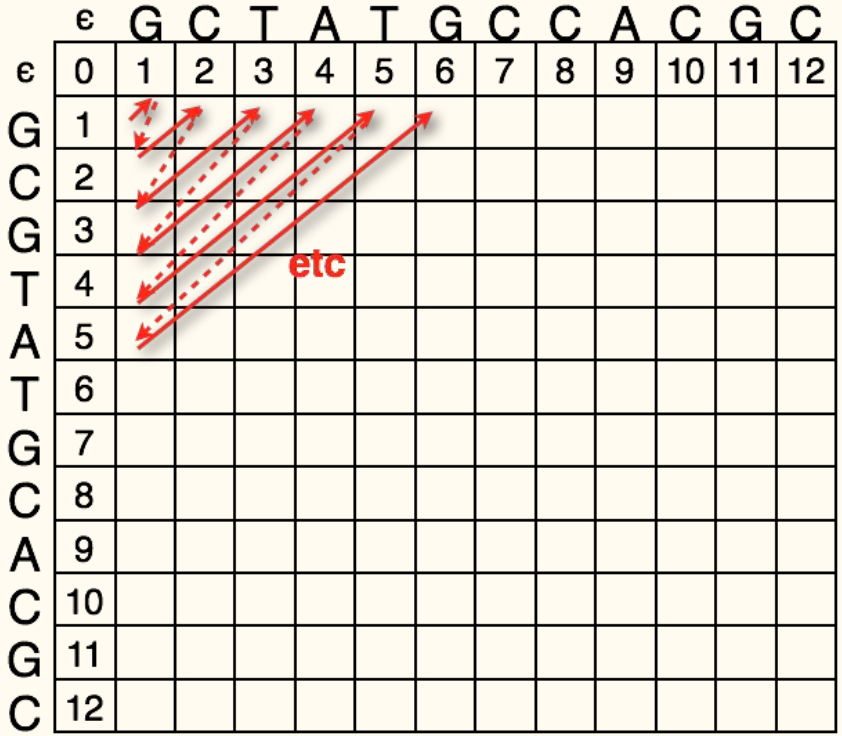
Fill remaining cells from top row to bottom and from left to right

Edit distance for x, y

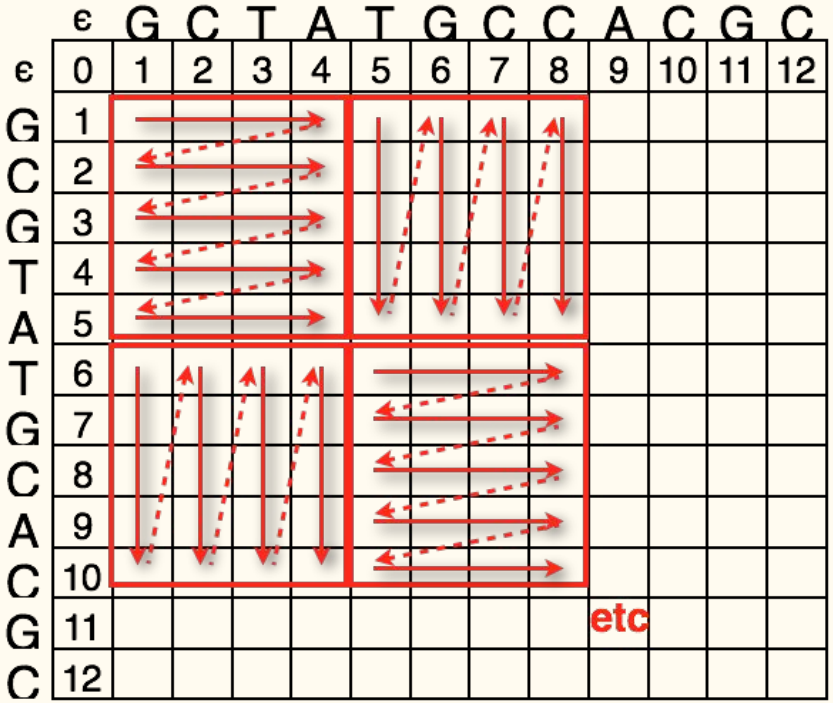
Filling up the matrix - vertically



Filling up the matrix - antidiagonal



Filling up the matrix - antidiagonal



Tabular computation - time complexity

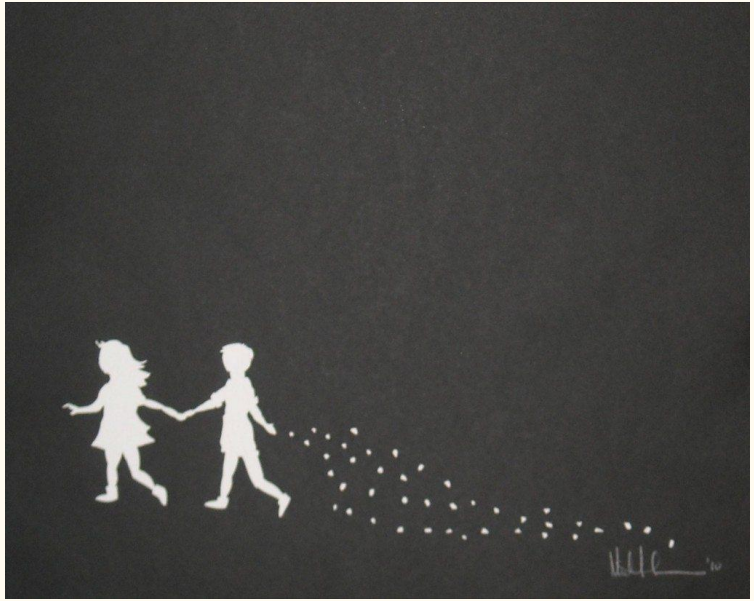
To calculate value of cell (i,j) we need to examine cells (i-1,j), (i,j-1), (i-1,j-1) and characters S1(i) and S2(j).

This is constant amount of time (per cell).

There are n x m cells, so it's O(nm) time.

Part 3: Traceback

- Leaving pointers during table computation so we can use them to find a way back (Hansel and Gretel/Ivica & Marica)
- We set a pointer from the cell(i,j) to the cell from which the value was computed



Part 3: Traceback

How do we get optimal edit transcript then? We traceback from cell (m,n) to (0,0) by using pointers which were set while the table is computed.

- (During table computation) Set pointers from cell (i,j) to cell from where the value (of (i,j)) was computed
- Follow (any) path of pointers from cell(m,n) to cell(0,0)
- Generating edit transcript (for each edge in the path):
  a. Horizontal edge interpret as insertion (of S2(j) to S1*)
  b. Vertical edge interpret as deletion (of S1(i))
  c. Diagonal edge as match or substitution (depending if S1(i)=S2(j) or not)
- Traceback corresponds to optimal alignment/edit transcript

***Note**: S1 (or x) is reference, while S2 (or y) is read being compared to the reference.

Part 3: Traceback

Note: In all our examples/definitions for alignment S1 (or x) is reference, while S2 (or y) is read compared to the reference.

This is important when retrieving edit transcript from traceback through table.
When we define horizontal movement/edge as insertion, it needs to be defined with respect to which string is on the horizontal and which is on the vertical axis of the table. Typically reference (S1) is on the vertical and read (S2) is on horizontal axis.

This is important because we can always define edit either as insertion in S1 or as deletion from S2, so it's important to know which string is the reference in order to be consistent.

Traceback

$D(i,j)$			w	r	i	t	e	r	s
		0	1	2	3	4	5	6	7
	0	0	← 1	← 2	←3	← 4	← 5	← 6	← 7
v	1	↑ 1	↖ 1	↖ ← 2	↖ ←3	↖ ← 4	↖ ← 5	↖ ← 6	↖ ← 7
i	2	↑ 2	↖ ↑ 2	↖ 2	↖ 2	← 3	← 4	← 5	← 6
n	3	↑ 3	↖ ↑ 3	↖ ↑ 3	↖ ↑3	↖ 3	↖ ← 4	↖ ← 5	↖ ← 6
t	4	↑ 4	↖ ↑ 4	↖ ↑ 4	↖ ↑4	↖ 3	↖ ← 4	↖ ← 5	↖ ← 6
n	5	↑ 5	↖ ↑ 5	↖ ↑ 5	↖ ↑5	↑ 4	↖ 4	↖ ← 5	↖ ← 6
e	6	↑ 6	↖ ↑ 6	↖ ↑ 6	↖ ↑6	↑ 5	↖ 4	↖ ← 5	↖ ← 6
r	7	↑ 7	↖ ↑ 7	↖ 6	↖ ← ↑7	↑ 6	↑ 5	↖ 4	← 5

Possible alignments:

S1: v i n t n e r
S2: w r i t e r s

v _ i n t n e r _
w r i _ t _ e r s

_ v i n t n e r _
w r i _ t _ e r s

Taken from D. Gusfield: Algorithms on strings, trees and sequences

Part 3: Traceback

How do we get optimal edit transcript then? We traceback from cell (m,n) to (0,0) by using pointers which were set while the table is computed.

What if there are multiple pointers pointing from the cell?

- If there is more than one pointer from the cell, pick any
  a. Each cell (except (0,0)) has a pointer out of it, you can't get stuck
  b. Any path from cell (m,n) to (0,0) represents optimal edit transcript
  c. Pointer allow all optimal edit transcripts to be retrieved

Traceback in practice

Without pointers: start at the end, at each step ask, which predecessor **gave** the minimum*

	ϵ	G	C	T	A	T	G	C	C	A	C	G	C
ϵ	0	1	2	3	4	5	6	7	8	9	10	11	12
G	1	0	1	2	3	4	5	6	7	8	9	10	11
C	2	1	0	1	2	3	4	5	6	7	8	9	10
G	3	2	1	1	2	3	3	4	5	6	7	8	9
T	4	3	2	1	2	2	3	4	5	6	7	8	9
A	5	4	3	2	1	2	3	4	5	5	6	7	8
T	6	5	4	3	2	1	2	3	4	5	6	7	8
G	7	6	5	4	3	2	1	2	3	4	5	6	7
C	8	7	6	5	4	3	2	1	2	3	4	5	6
A	9	8	7	6	5	4	3	2	2	2	3	4	5
C	10	9	8	7	6	5	4	3	2	3	2	3	4
G	11	10	9	8	7	6	5	4	3	3	3	2	3
C	12	11	10	9	8	7	6	5	4	4	3	3	2

A: From here

Q: How did I get here?

*Note: This does **not mean** "which predecessor has the minimum value". It means we need to calculate which predecessor **gave** the minimum (value of our current cell). That is: which predecessor plus the edit operation penalty needed for moving from this predecessor to current cell gives the minimal (current) cell value.

Traceback in practice

Without pointers: start at the end, at each step ask, which predecessor gave the minimum

	ϵ	G	C	T	A	T	G	C	C	A	C	G	C
ϵ	0	1	2	3	4	5	6	7	8	9	10	11	12
G	1	0	1	2	3	4	5	6	7	8	9	10	11
C	2	1	0	1	2	3	4	5	6	7	8	9	10
G	3	2	1	1	2	3	3	4	5	6	7	8	9
T	4	3	2	1	2	2	3	4	5	6	7	8	9
A	5	4	3	2	1	2	3	4	5	5	6	7	8
T	6	5	4	3	2	1	2	3	4	5	6	7	8
G	7	6	5	4	3	2	1	2	3	4	5	6	7
C	8	7	6	5	4	3	2	1	2	3	4	5	6
A	9	8	7	6	5	4	3	2	2	2	3	4	5
C	10	9	8	7	6	5	4	3	2	3	2	3	4
G	11	10	9	8	7	6	5	4	3	3	3	2	3
C	12	11	10	9	8	7	6	5	4	4	3	3	2

A: From here

Q: How did I get here?

Traceback in practice

Without pointers: start at the end, at each step ask, which predecessor gave the minimum

	ϵ	G	C	T	A	T	G	C	C	A	C	G	C
ϵ	0	1	2	3	4	5	6	7	8	9	10	11	12
G	1	0	1	2	3	4	5	6	7	8	9	10	11
C	2	1	0	1	2	3	4	5	6	7	8	9	10
G	3	2	1	1	2	3	3	4	5	6	7	8	9
T	4	3	2	1	2	2	3	4	5	6	7	8	9
A	5	4	3	2	1	2	3	4	5	5	6	7	8
T	6	5	4	3	2	1	2	3	4	5	6	7	8
G	7	6	5	4	3	2	1	2	3	4	5	6	7
C	8	7	6	5	4	3	2	1	2	3	4	5	6
A	9	8	7	6	5	4	3	2	2	2	3	4	5
C	10	9	8	7	6	5	4	3	2	3	2	3	4
G	11	10	9	8	7	6	5	4	3	3	3	2	3
C	12	11	10	9	8	7	6	5	4	4	3	3	2

A: From here

Q: How did I get here?

Traceback in practice

Without pointers: start at the end, at each step ask, which predecessor gave the minimum.
Path corresponds to edit transcript.

	ϵ	G	C	T	A	T	G	C	C	A	C	G	C
ϵ	0	1	2	3	4	5	6	7	8	9	10	11	12
G	1	0	1	2	3	4	5	6	7	8	9	10	11
C	2	1	0	1	2	3	4	5	6	7	8	9	10
G	3	2	1	1	2	3	3	4	5	6	7	8	9
T	4	3	2	1	2	2	3	4	5	6	7	8	9
A	5	4	3	2	1	2	3	4	5	5	6	7	8
T	6	5	4	3	2	1	2	3	4	5	6	7	8
G	7	6	5	4	3	2	1	2	3	4	5	6	7
C	8	7	6	5	4	3	2	1	2	3	4	5	6
A	9	8	7	6	5	4	3	2	2	2	3	4	5
C	10	9	8	7	6	5	4	3	2	3	2	3	4
G	11	10	9	8	7	6	5	4	3	3	3	2	3
C	12	11	10	9	8	7	6	5	4	4	3	3	2

Alignment:

```
GCGTATG-CACGC
||  ||||  |||||
GC-TATGCCACGC
```

Edit transcript:

MMDMMMMIMMMMM

Traceback complexity

If the table is already filled, retrieving optimal edit transcript can be computed in O(n+m) time.

Any cooptimal edit transcript can also be calculated in O(n+m) time.

Bottom up computation - summary

Matrix-filling dynamic programming algorithm is O(mn) time and space:

- Filling matrix is O(mn) space and time, and yields edit distance
- Backtrace is O(m + n) time, yields optimal alignment / edit transcript

Acknowledgment

Slides/pictures on some of the slides used with permission from Ben Langmead from John Hopkins university.

Global alignment

—

Weighted edit distance and global (end-to-end) alignment

Weighted edit distance

In nature, not all edit operations are of the same frequency and impact:
Gaps (insertions, deletions) are more severe than simple mismatch. Mismatch can be result of sequencing error (gap cannot). Also, not all mismatches are the same (ti/tv ratio).

Operation weighted edit-distance

- Associating cost with every edit-operation

This is achieved by adjusting penalties, and giving different scores to every **edit operation (operation weighted edit distance).**

We minimize on total operation weight.

Operation weighted edit distance

Important note:
Since substitution can be modeled as deletion followed by insertion, is substitutions are allowed, keep in mind that substitution should be less penalized than deletion plus insertion.

```
CTCAGG  vs  CTCA_GG
CTCTGG      CTC_ TGG
```

Operation weighted edit distance

Usually we use same scores for insertion/deletion (d), and specific for match (e) and mismatch (r) operation.

Base conditions:

$$D(i,0)=i\times d$$

$$D(0,j)=j\times d$$

and recurrence relation:

$$D(i,j)=\min\,[D(i-1,j)+d,\ D(i,\ j-1)+d,\ D(i-1,j-1)+\delta(i,j)],\ \text{where}$$

$\delta(i,j)=r$ if $S1[i-1]\neq S2[j-1]$, else if $S1[i-1]=S2[j-1]$, $\delta(i,j)=e$.

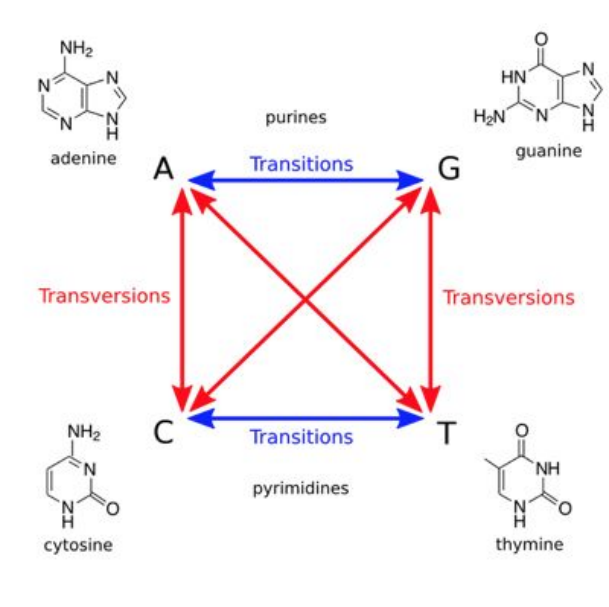
Operation weighted edit distance

Algorithmic complexity stays the same, and it's O(nm).

Alphabet weighted edit distance

...also, not all mismatches are the same (ti/tv ratio). A to T is more costly than A to C. For indels, we want to weight by which character is being inserted/deleted.

Human *transition to transversion ratio* (AKA *ti/tv*) is ~2.1



Alphabet weighted edit distance

Solution: We score exactly on we add *alphabet-weighted* edit distance.

Note: weight depends on characters involved but not on where the characters appear in string.

Weighted edit distance

Alphabet weighted:

- Used in protein comparison
- PAM and BLOSUM scoring matrices - usually defined in maximizing (similarity) terms

- DNA strings comparison - mostly unweight or operation weight
  - Example: BLAST - match +5, mismatch -4

String similarity (global alignment)

More oftenly used way of representing string relatedness is to measure string similarity (instead of distance). - this will be much clearer in the next lesson (local alignment).

We need to score alignment in such way that every pair (position) in the alignment is given the score, and then the score of alignment is represented as the sum of scores for every position in the alignment.

String similarity (global alignment)

(Global) alignment of two strings S1 and S2 is obtained by first inserting chosen spaces (or dashes) either into (or at the end of) S1 or S2 and then placing one resulting string above the other so that so that every character (or space) in one string is opposite a unique character (or space) in another string.

- An alternative way (to edit transcript) to represent transformation of one string to another

```
v_intner_
wri_t_ers
```

Remember from the previous lecture comparison of alignment and edit transcript!

String similarity (more formally)

Def 1: (scoring letter pairs): Let $\sum$ be alphabet used for strings S1 and S2, and let $\sum$' be $\sum$ with added character "_" denoting a space. Then, for any two characters x, y in $\sum$', s(x,y) denotes the value (or *score*) obtained by aligning character x against character y.

Def 2 (alignment score): For given alignment A of S1 and S2, let S1' and S2' denote strings after the chosen insertion of spaces, and let l denote the (equal) length of two strings S1' and S2' in A. The value of alignment A is defined as $\sum_{i=1}^{l} s(S1'(i), S2'(i))$

String similarity (global alignment)

Example: $\Sigma = \{a,b,c,d\}$, scoring function (matrix)

s	a	b	c	d	_
a	1	-1	-2	0	-1
b		3	-2	-1	0
c			0	-4	-2
d				3	-1
_					0

Alignment:

c a c _ d b d
c a b b d b _

Value of alignment score: $0+1 -2 +0 + 3 +3 -1 = 4$

Global alignment

In practice, we set values in scoring matrix such that they are positive (or equal to zero) for match and negative for mismatch. Then we try to maximize alignment value (as stated on begging of this lecture).

$s(a, b)$:

	A	C	G	T	-
A	1	-3	-1	-3	-7
C	-3	1	-3	-1	-7
G	-1	-3	1	-3	-7
T	-3	-1	-3	1	-7
-	-7	-7	-7	-7	

gaps in a

gaps in b

-1	*Transitions* (A↔ G, C↔T)
-3	*Transversions* (everything else)
-7	*Gaps*

Example: Scoring function reflecting that transitions are more common than transversions and mismatches are more common than gaps.

Global alignment

Def: Given a pairwise scoring matrix over the alphabet Σ', the similarity of two strings S1 and S2 is identified as the value of the alignment A of S1 and S2 that maximizes total alignment value. This is also called *optimal alignment* of S1 and S2.

Global alignment is also called Needleman-Wunsch alignment.

Global alignment

V(i,j): value of the optimal alignment for prefixes *S1*[1...i] and *S2*[1...j]

Base conditions:

$$V(0,j)=\sum_{1\leq j\leq k} s(\text{'\_'}, S2(j-1))$$

$$V(i,0)=\sum_{1\leq j\leq k} s(S1(i-1),\text{'\_'})$$

And recurrence relation:

V(i,j)=max[V(i-1, j)+s(S1(i-1), '_'), V(i, j-1)+s('_', S2(j-1)), V(i-1, j-1)+s(S1(i-1), S2(j-1))]

Global alignment

X \ Y	ε	T	A	T	G	T	C	A	T	G	C
ε	0	-7	-14	-21	-28	-35	-42	-49	-56	-63	-70
T	-7	1	-6	-13	-20	-27	-34	-41	-48	-55	-62
A	-14	-6	2	-5	-12	-19	-26	-33	-40	-47	-54
C	-21	-13	-5	1	-6	-13	-18	-25	-32	-39	-46
G	-28	-20	-12	-6	2	-5	-12	-19	-26	-31	-38
T	-35	-27	-19	-11	-5	3	-4	-11	-18	-25	-32
C	-42	-34	-26	-18	-12	-4	4	-3	-10	-17	-24
A	-49	-41	-33	-25	-19	-11	-3	5	-2	-9	-16
G	-56	-48	-40	-32	-24	-18	-10	-2	2	-1	-8
C	-63	-55	-47	-39	-31	-25	-17	-9	-3	-1	0

$s(a, b)$

	A	C	G	T	-
A	1	-3	-1	-3	-7
C	-3	1	-3	-1	-7
G	-1	-3	1	-3	-7
T	-3	-1	-3	1	-7
-	-7	-7	-7	-7	

Optimal global alignment value

Global alignment

		Y									
	ε	T	A	T	G	T	C	A	T	G	C
ε	0	-7	-14	-21	-28	-35	-42	-49	-56	-63	-70
T	-7	1	-6	-13	-20	-27	-34	-41	-48	-55	-62
A	-14	-6	2	-5	-12	-19	-26	-33	-40	-47	-54
C	-21	-13	-5	1	-6	-13	-18	-25	-32	-39	-46
X G	-28	-20	-12	-6	2	-5	-12	-19	-26	-31	-38
T	-35	-27	-19	-11	-5	3	-4	-11	-18	-25	-32
C	-42	-34	-26	-18	-12	-4	4	-3	-10	-17	-24
A	-49	-41	-33	-25	-19	-11	-3	5	-2	-9	-16
G	-56	-48	-40	-32	-24	-18	-10	-2	2	-1	-8
C	-63	-55	-47	-39	-31	-25	-17	-9	-3	-1	0

```
TACGTCA-GC
||  | | | |  ||
TATGTCATGC
```

-1 (transition) -7 (gap)

Global alignment vs weighted edit distance

Yes we can: just invert scoring matrix (larger score for similarity, smaller for difference) and minimize instead of maximize (in recurrence relation).

$s(a, b)$

	A	C	G	T	-
A	1	-3	-1	-3	-7
C	-3	1	-3	-1	-7
G	-1	-3	1	-3	-7
T	-3	-1	-3	1	-7
-	-7	-7	-7	-7	

...as long as we switch max to min:

	A	C	G	T	-
A	0	4	2	4	8
C	4	0	4	2	8
G	2	4	0	4	8
T	4	2	4	0	8
-	8	8	8	8	

Global alignment

	ε	T	A	T	G	T	C	A	T	G	C
ε	0	8	16	24	32	40	48	56	64	72	80
T	8	0	8	16	24	32	40	48	56	64	72
A	16	8	0	8	16	24	32	40	48	56	64
C	24	16	8	2	10	18	24	32	40	48	56
G	32	24	16	10	2	10	18	26	34	40	48
T	40	32	24	16	10	2	10	18	26	34	42
C	48	40	32	24	18	10	2	10	18	26	34
A	56	48	40	32	26	18	10	2	10	18	26
G	64	56	48	40	32	26	18	10	6	10	18
C	72	64	56	48	40	34	26	18	12	10	10

	A	C	G	T	-
A	0	4	2	4	8
C	4	0	4	2	8
G	2	4	0	4	8
T	4	2	4	0	8
-	8	8	8	8	

Optimal global alignment value

Global alignment vs weighted edit distance

X \ Y	ϵ	T	A	T	G	T	C	A	T	G	C
ϵ	0	8	16	24	32	40	48	56	64	72	80
T	8	0	8	16	24	32	40	48	56	64	72
A	16	8	0	8	16	24	32	40	48	56	64
C	24	16	8	2	10	18	24	32	40	48	56
G	32	24	16	10	2	10	18	26	34	40	48
T	40	32	24	16	10	2	10	18	26	34	42
C	48	40	32	24	18	10	2	10	18	26	34
A	56	48	40	32	26	18	10	2	10	18	26
G	64	56	48	40	32	26	18	10	6	10	18
C	72	64	56	48	40	34	26	18	12	10	10

$s(a, b)$

	A	C	G	T	-
A	0	4	2	4	8
C	4	0	4	2	8
G	2	4	0	4	8
T	4	2	4	0	8
-	8	8	8	8	

Same backtrace

Global alignment - complexity

Matrix-filling dynamic programming algorithm is O(mn) time and space

- Filling matrix is O(mn) space and time, and yields global alignment value
- Traceback is O(m + n) steps, yields optimal alignment / edit transcript

Global alignment - scoring schema

We can set scores how we like.

We can have mix of positive and negative scores. In the dynamic programming we can *maximize* a similarity score or *minimize* a dissimilarity penalty.