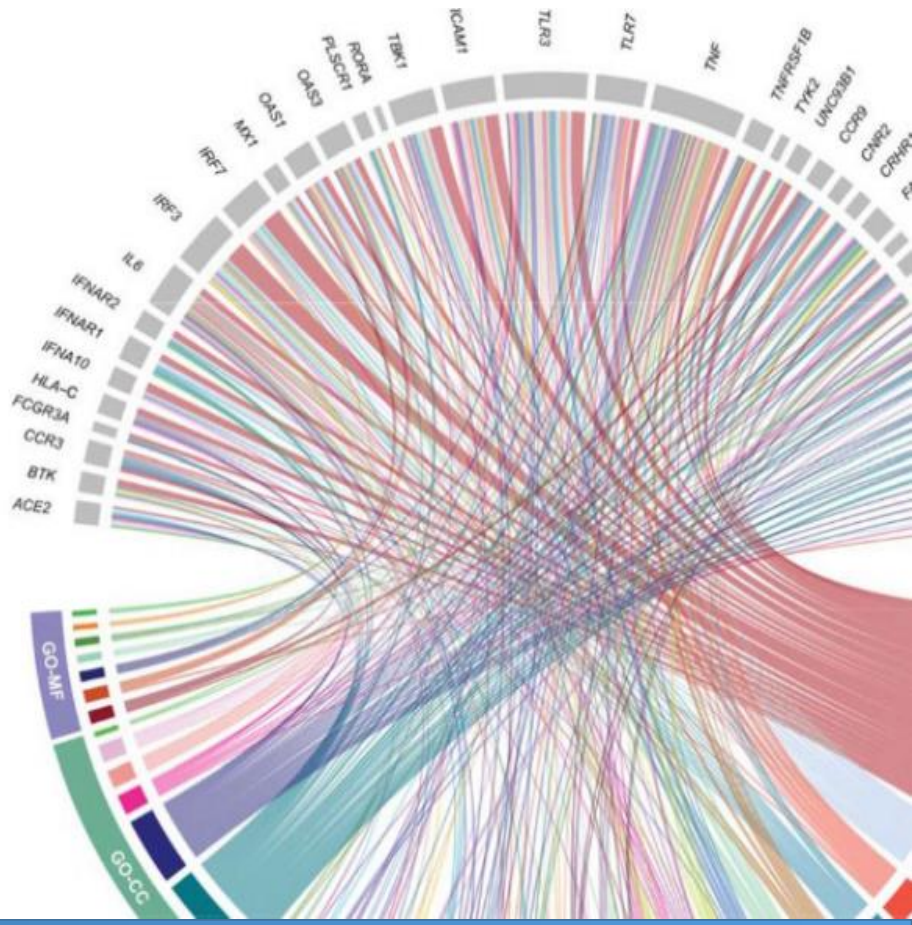
Tècniques i Eines Bioinformàtiques

Approximate String Matching



Santiago Marco-Sola (santiago.marco@upc.edu)

Màster en Enginyeria Informàtica, UPC
Departament of Computer Science
Facultat d'Informàtica de Barcelona (FIB), UPC

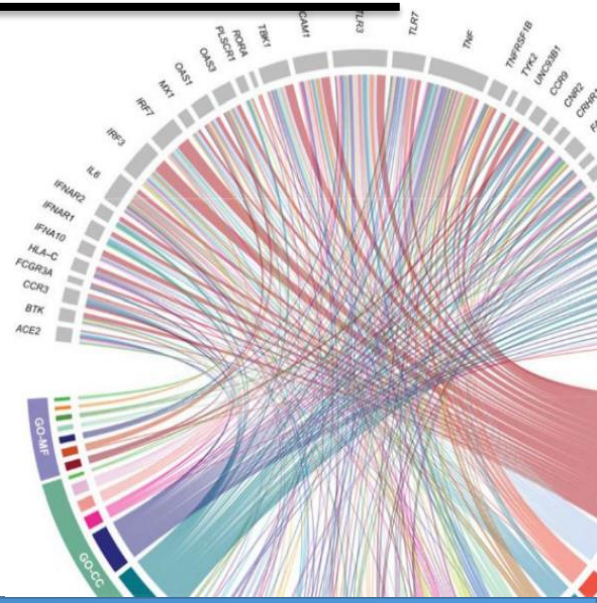
Acknowledgements

Many pictures and materials are taken from **Ben Langmead's course**.

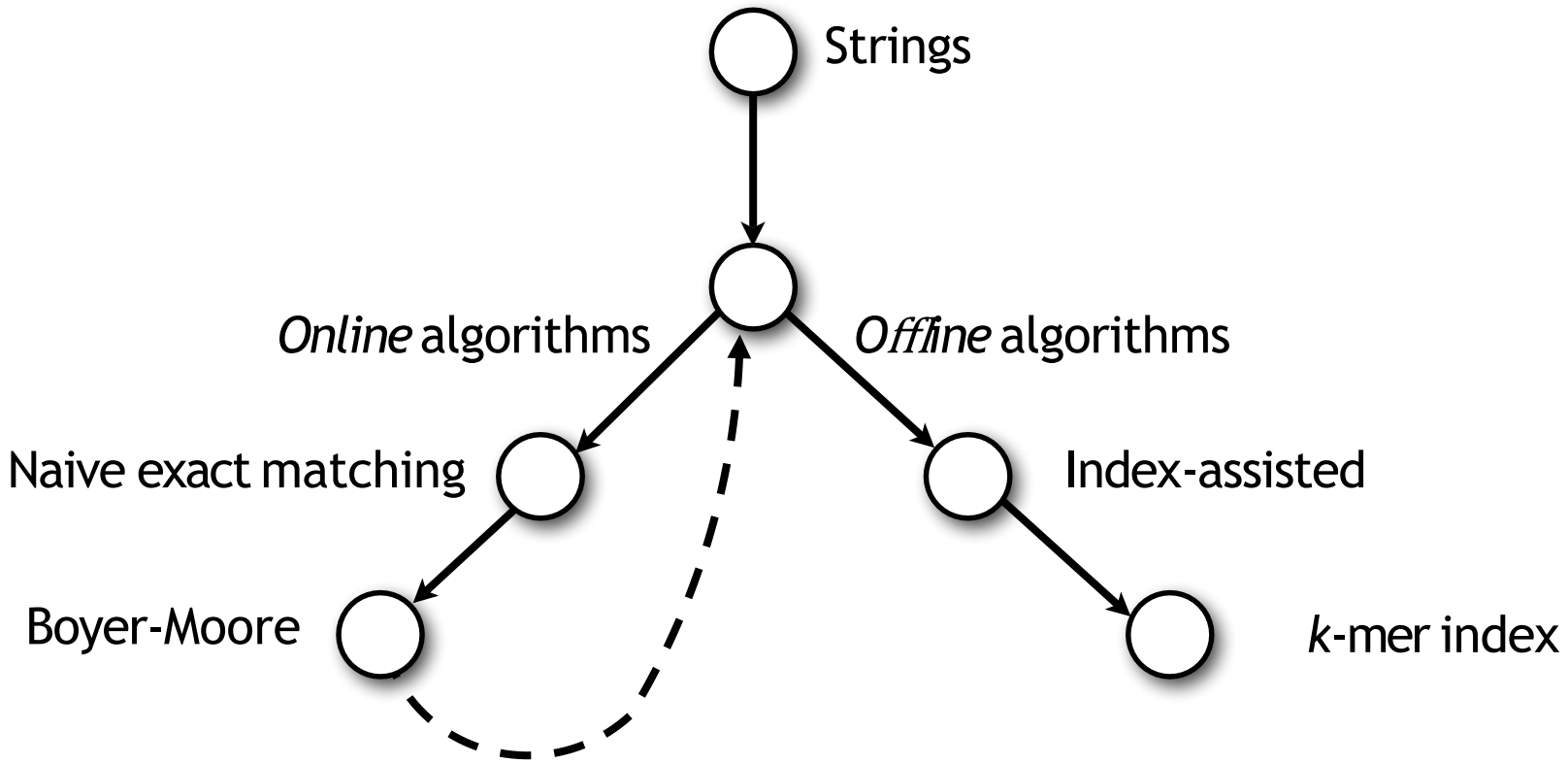
Course heavily inspired in:

- **Genome-Scale Algorithm Design**. Veli Mäkinen, Djamal Belazzougui, Fabio Cunial, Alexandru I. Tomescu. Cambridge University Press.
- **Algorithms on Strings, Trees, and Sequences**. Dan Gusfield. Cambridge University Press.
- **An Introduction to Bioinformatics Algorithms.** Neil C. Jones, Pavel A. Pevzner. MIT Press.

1 Approximate String Matching



Approximate matching



We have focused on *exact* matching…

… in reality, we have to deal with *differences*

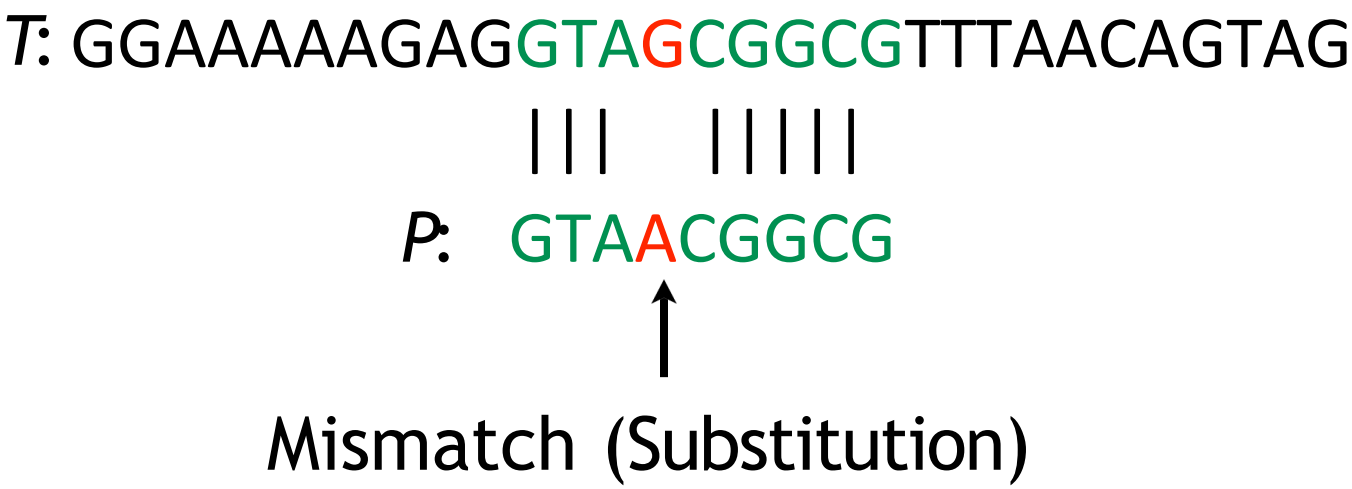
Read CTCAAACTCCTGACCTTTGGTGATCCACCCGCCTNGGCCTTC

Reference

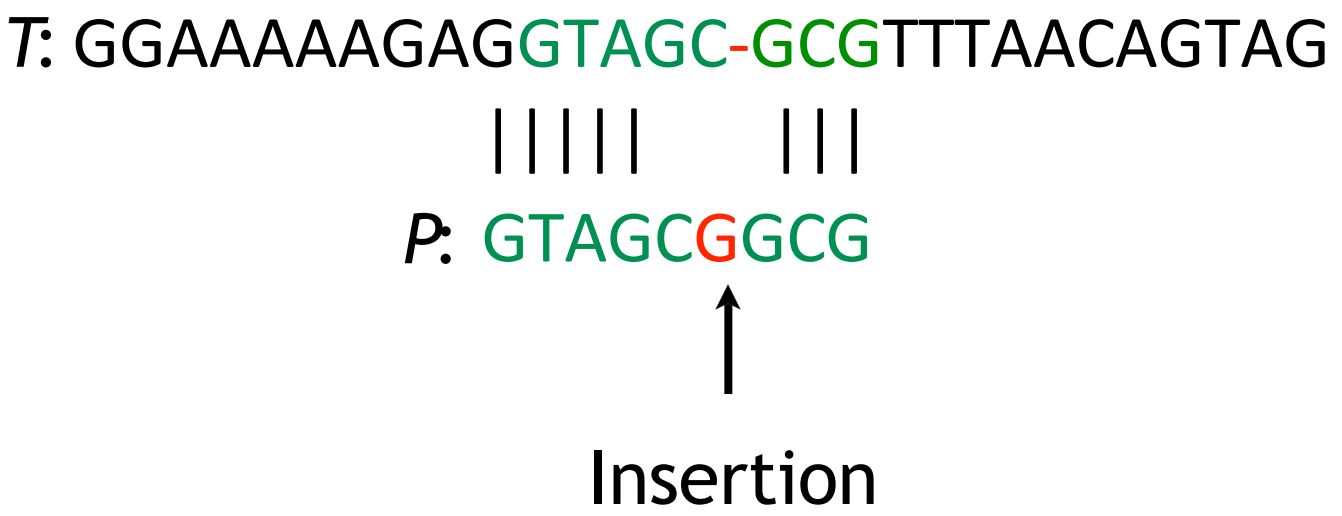
Sequence differences occur because of…

1. Sequencing error
2. Genetic variation

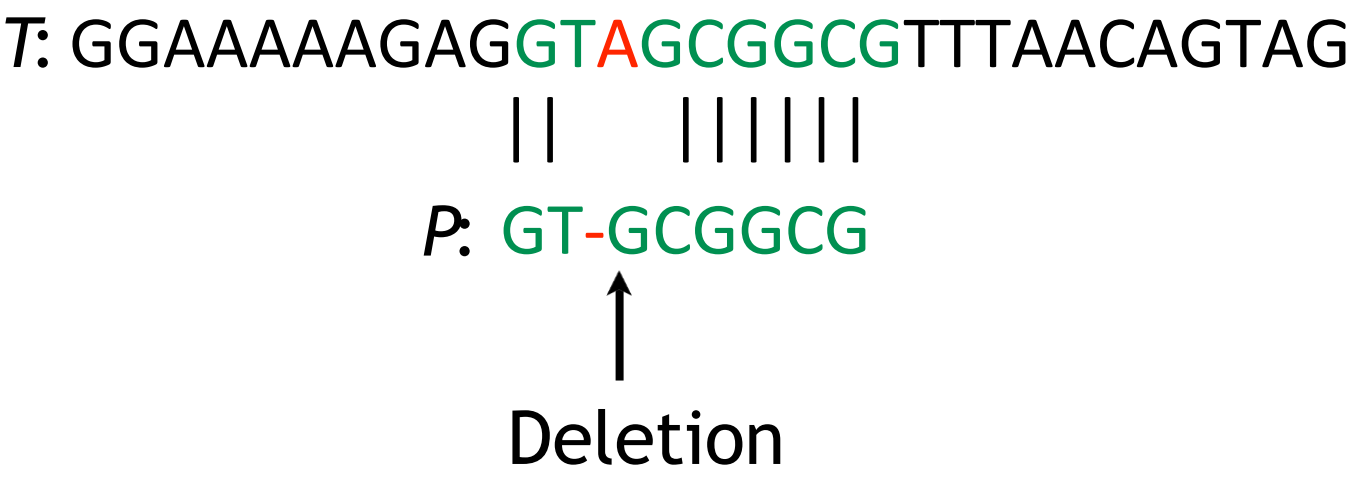
Approximate matching



Approximate matching



Approximate matching



Hamming distance

For *X* & *Y* where |*X* |= |*Y* |, *hamming distance* = minimum # substitutions needed to turn one into the other

Hamming distance = 3

Edit distance

(AKA Levenshtein distance)

For *X* & *Y*, *edit distance* = minimum # edits (substitutions, insertions, deletions) needed to turn one into the other

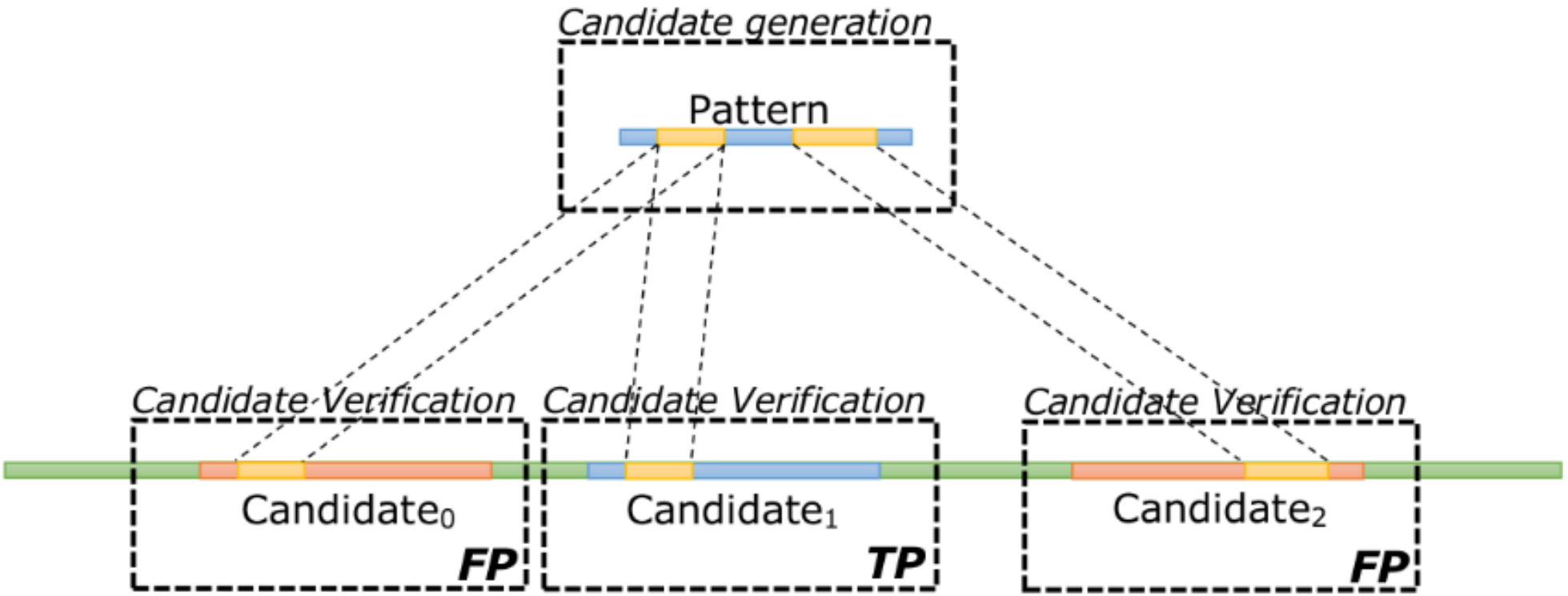
```
X: T G G C C G C G C A A A A A C A G C
   | |   | | | | | | | | |   | | | |
Y: T G A C C G C G C A A A A - C A G C
```

Edit distance = 2

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

Edit distance = 2

Approximate String Matching



Exercises

Hamming sequence search in reference

- Implement a program that, given a reference sequence, searches a match for an input sequence up to m mismatches using Hamming distance.

Example

```
> \time -v python3 search_hamming.py -r ../../data/chr1.fa -i GAGCAATAAATT -m 2

Reading input FASTA ... read 248956422 bases from '../../data/chr1.fa'.
Searching 'GAGCAATAAATT' sequence ...
Found 9167 exact matches in 242.365 s.
```

Exercises

Hamming sequence search in reference

- Implement a program that, given a reference sequence, searches a match for an input sequence up to m mismatches using Hamming distance.

Code

```
def hamming_distance(seq1, seq2):
  """Compute the Hamming distance between two sequences of equal length."""
  if len(seq1) != len(seq2):
    raise ValueError("Sequences must be of the same length")
  distance = 0
  for i in range(len(seq1)):
    if seq1[i] != seq2[i]:
      distance += 1
  return distance
```

Exercises

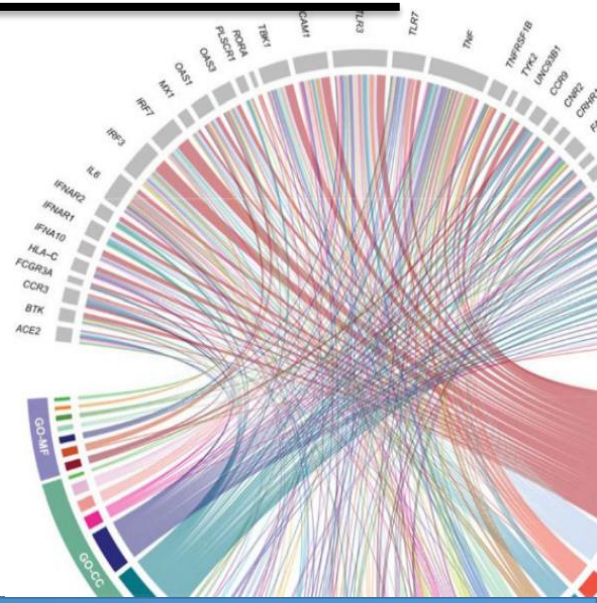
Hamming sequence search in reference

- Implement a program that, given a reference sequence, searches a match for an input sequence up to m mismatches using Hamming distance.

Code

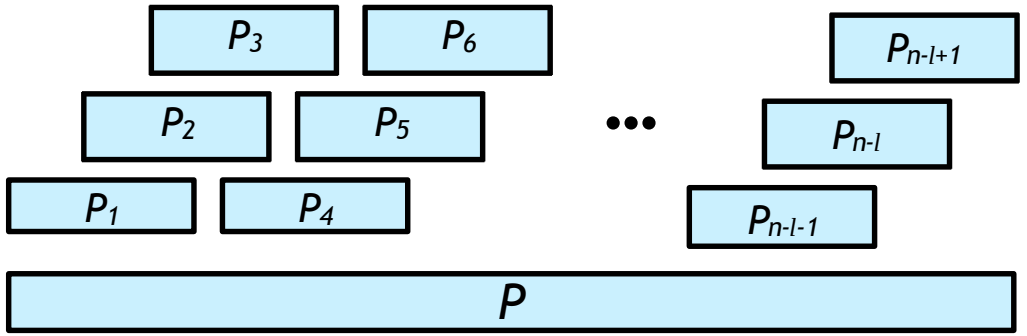
```
def search_sequence(reference, sequence, m):
  start_time = time.time()
  matches = []
  for i in range(0,len(reference)-len(sequence)):
    if hamming_distance(reference[i:i+len(sequence)],sequence) <= m:
      matches.append(i)
  end_time = time.time()
  # Print Results
  print("Found %d exact matches in %2.3f s." % (len(matches),end_time-start_time))
  for match in matches:
    print("%d " % match,end="")
```

2 K-mer Seeding

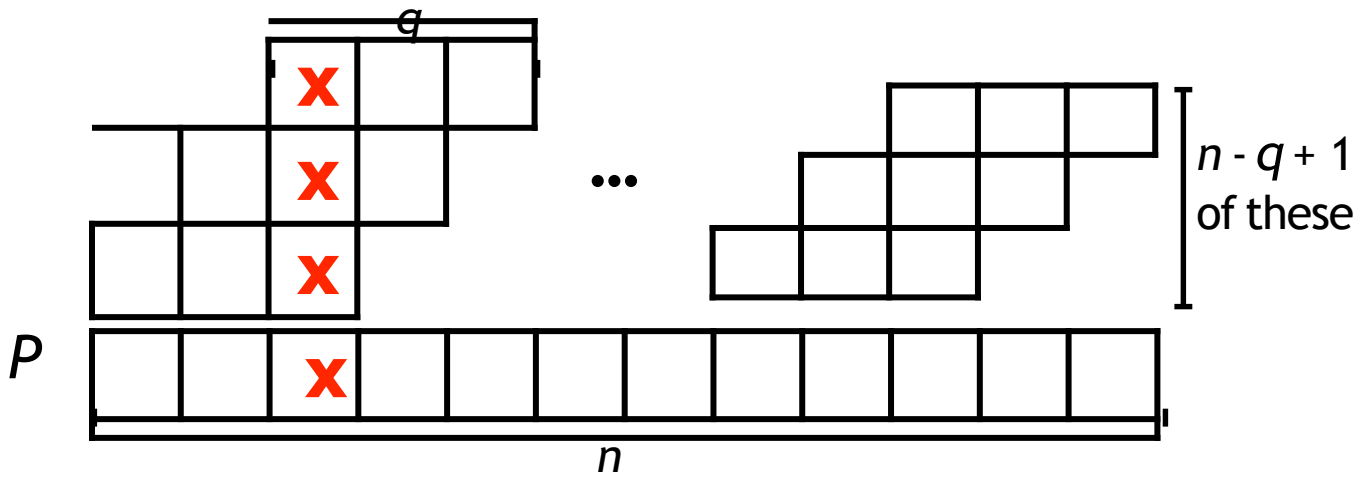


Overlapping K-mers

Now consider *overlapping* substrings



Q-gram Lemma



Say substrings are length *q*. There are *n* - *q* + 1 such substrings.

1 edit to *P* changes *at most q* substrings

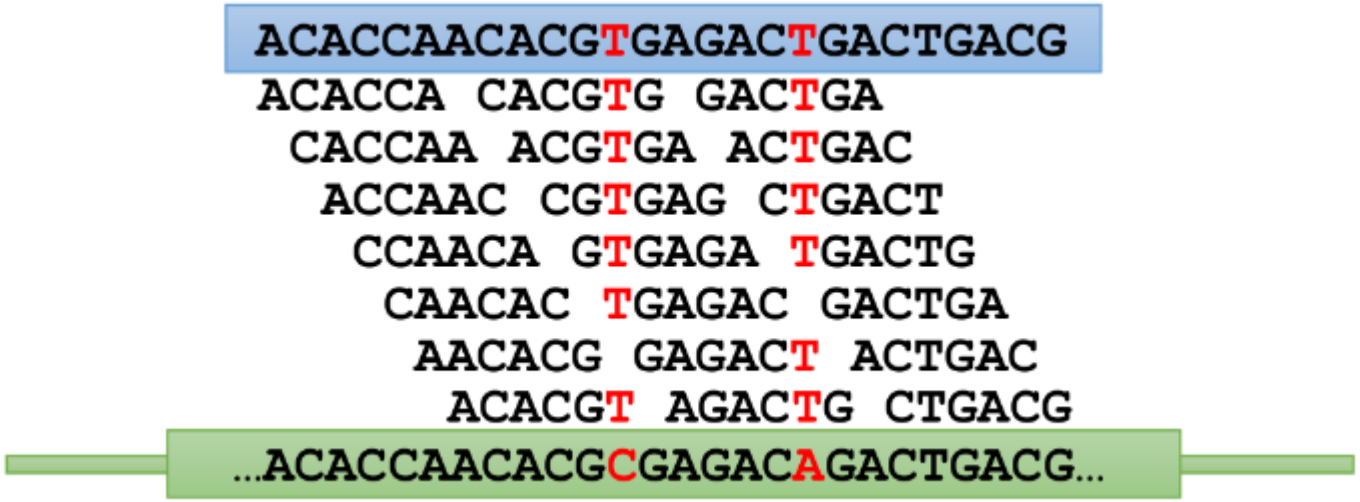
kq is *worst case;*
could be < *kq*

Minimum # of length-*q* substrings unedited after *k* edits? $n - q + 1 - kq$

***q-gram* lemma**: if *P* occurs in *T* with up to *k* edits, alignment must contain *t* exact matches of length *q*, where $t \geq n - q + 1 - kq$

Approximate string matching using Q-gram Lemma

- If P occurs in T with up to k edits, alignment contains an exact match of length q, where q ≥ floor(n / (k + 1))
  - Obtained by solving for q: n - q + 1 - kq ≥ 1
- Exact matching filter
  - Find matches of length floor(n / (k + 1)) between T and any substring of P. Check vicinity for full match.



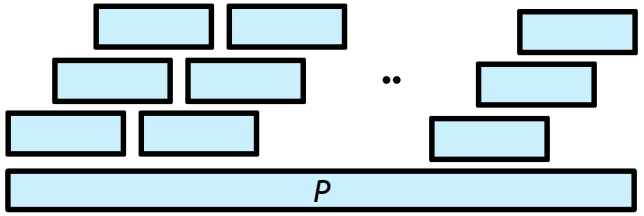
Lemma 5.3.2 (q-gram lemma). Given P, e, and $d()$, if the candidate w aligns the pattern P (i.e. $d(w, P) \leq e$) then P and w share at least $|w| + 1 - |q| \times (e + 1)$ common q-grams.

Sensitivity

Sensitivity = fraction of "true" approximate matches discovered by the algorithm

Lossless algorithm finds all of them, *lossy* algorithm doesn't necessarily

We've seen *lossless* algorithms. Most everyday tools are *lossy*. Lossy algorithms are usually much speedier & still acceptably sensitive.



Example lossy algorithm: pick $q > floor(n / (k + 1))$

Exercises

1. Sequence comparison by counting k-mers

- Given 2 sequences, m (maximum number of mismatches), and q (kmer length) use the q-gram lemma to compare the sequences and assess if they could match.

Code

```
from collections import Counter

def q_gram_match(T, P, q, m):
    """Uses the q-gram lemma to assess if P occurs in T with at most k edits."""
    n = len(P)
    num_qgrams_needed = max(1, n - q + 1 - m * q)  # Minimum q-gram matches required
    # Generate q-grams for P
    P_qgrams = [P[i:i+q] for i in range(len(P) - q + 1)]
    P_qgram_counts = Counter(P_qgrams)
    # Generate q-grams for T
    T_qgrams = [T[i:i+q] for i in range(len(T) - q + 1)]
    T_qgram_counts = Counter(T_qgrams)
    # Count how many q-grams in P appear in T
    matching_qgrams = \
      sum(min(P_qgram_counts[qgram], T_qgram_counts.get(qgram, 0)) for qgram in P_qgram_counts)
    # Decision based on q-gram lemma
    return matching_qgrams >= num_qgrams_needed
```

Exercises

1. Sequence comparison by counting k-mers

- Given 2 sequences, m (maximum number of mismatches), and q (kmer length) use the q-gram lemma to compare the sequences and assess if they could match.

Code

```
# Example Usage:
T = "GATCACAGGTCTATCACCCTATTAACCACT"
#            ||| ||||||  ||
P =         "GGTGTATCACTCT"
q = 3
m = 1

result = q_gram_match(T, P, q, m)
print(f"Does P appear in T with ≤ {m} edits? {result}")
```

Exercises

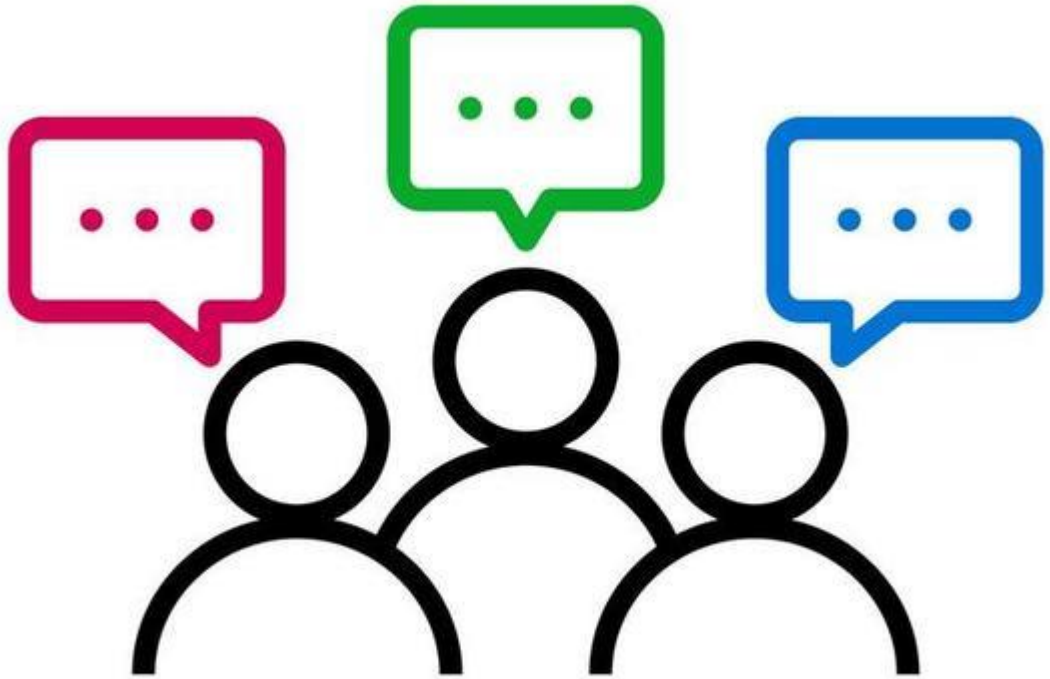
2. Online Approximate String Matching (using q-gram lemma)

- Improve the online search program to exploit the q-gram lemma and find all matches in the reference (chr1.fa) that match a given input-sequence with less than m mismatches.

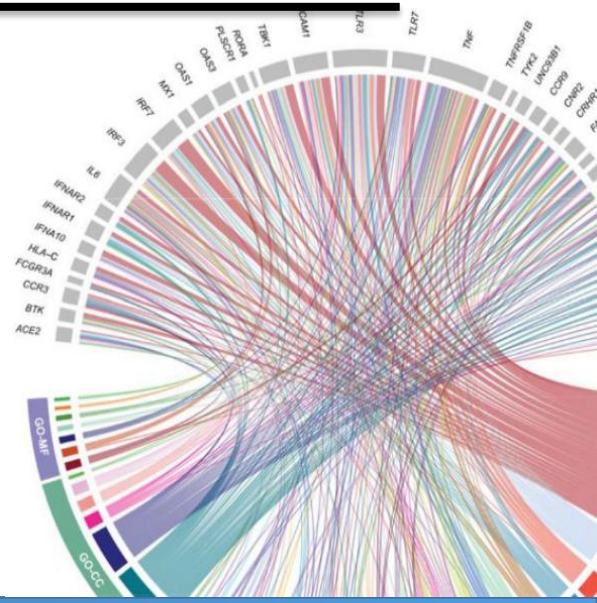
Exercises

3. Indexed Approximate String Matching (using q-gram lemma)

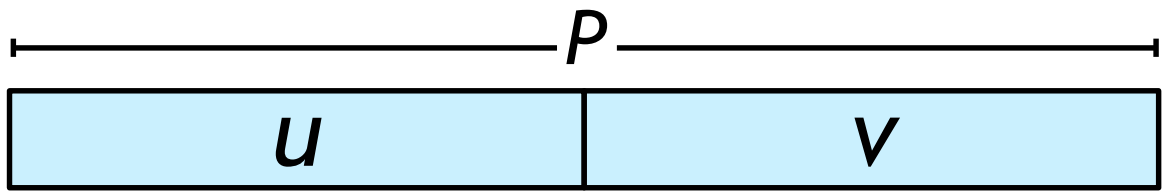
- Improve the kmer-hash based program to exploit the q-gram lemma and find all matches in the reference (chr1.fa) that match a given input-sequence with less than m mismatches.



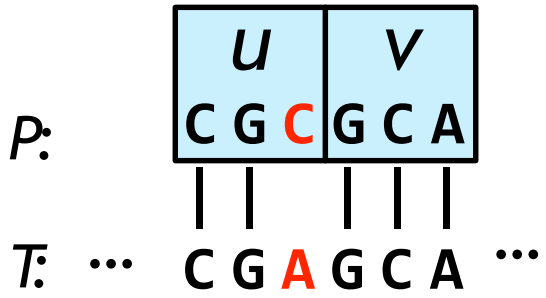
3 Factors Seeding

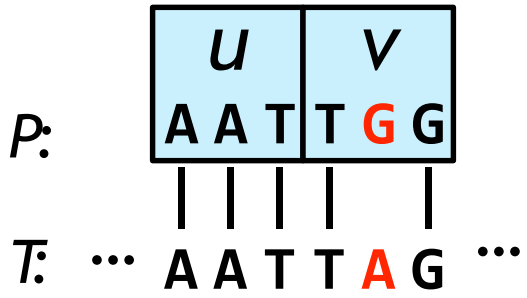


Approximate matching

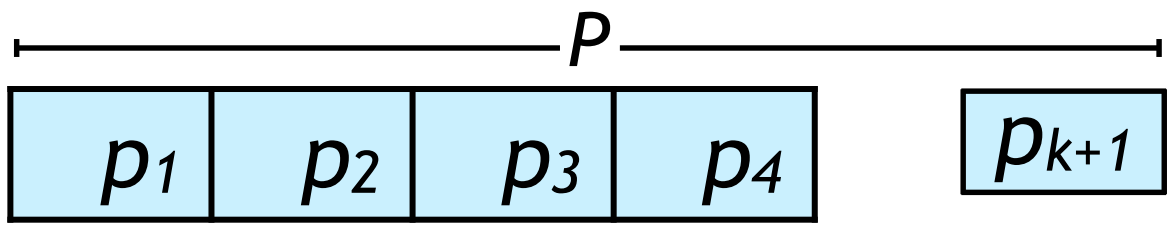


If P occurs in T with 1 edit, then u or v appears with no edits



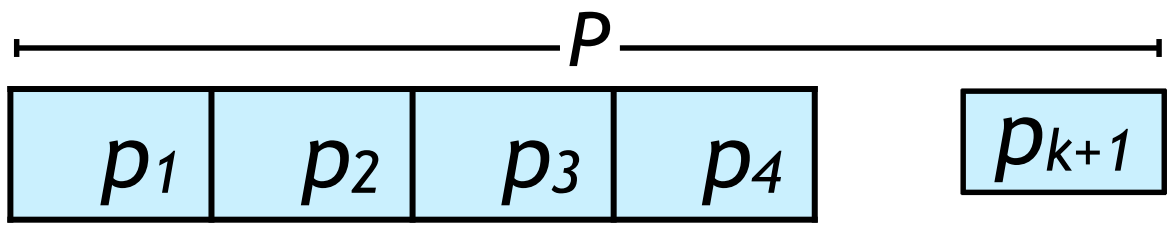


Approximate matching



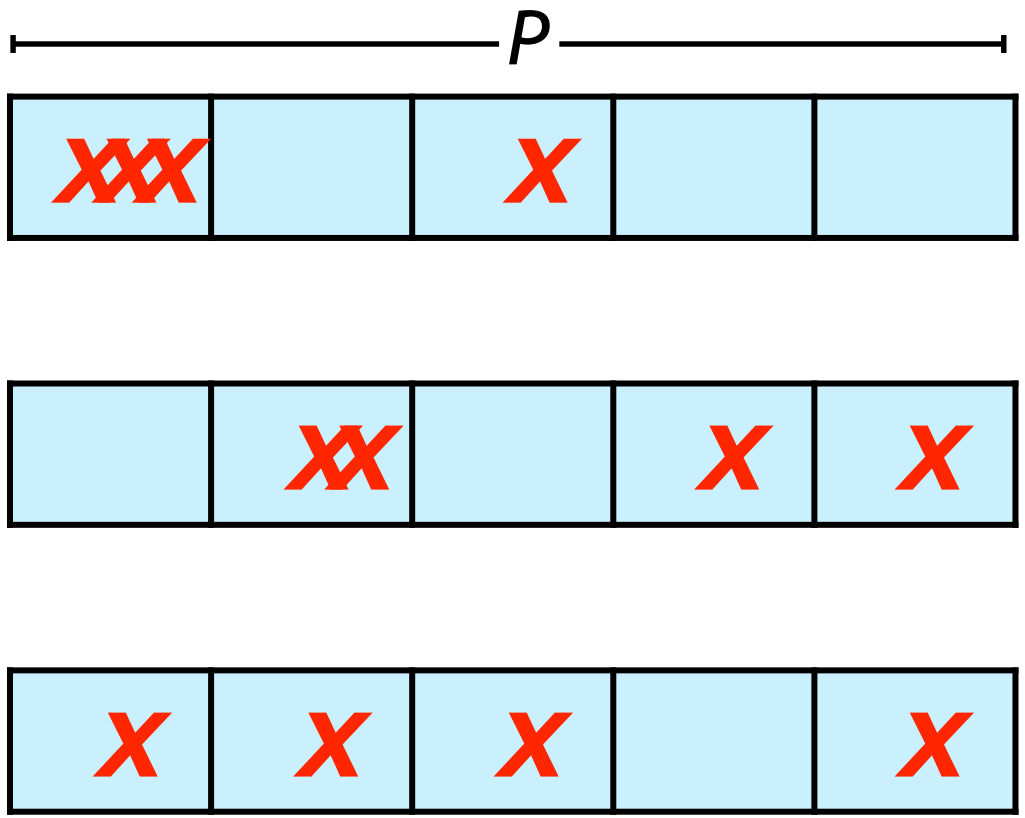
If *P* occurs in *T* with up to *k* edits...

Approximate matching



If P occurs in T with up to k edits, then at least one of $p_1, p_2, \ldots, p_{k+1}$ must appear with 0 edits

Approximate matching

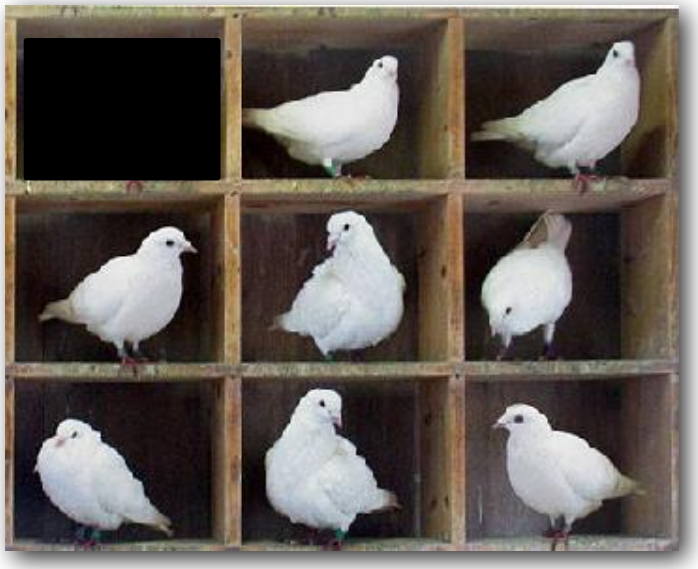


5 partitions
4 edits (*X*)

Approximate matching

Pigeonhole principle: *k+1* pigeons, *k* holes.
At least one has >1 pigeon!

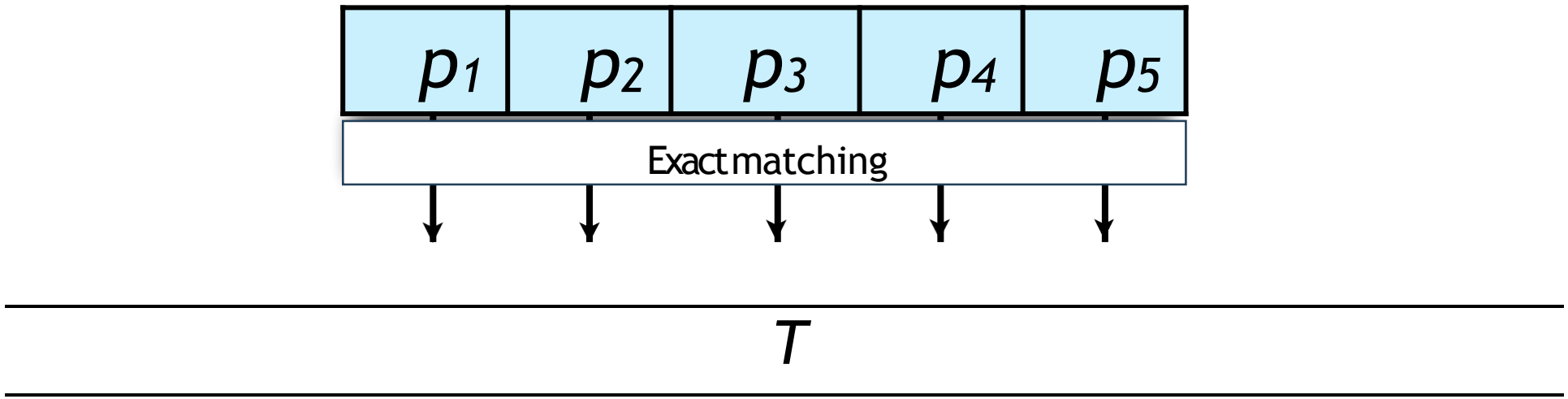
Approximate matching



We have *k* pigeons, *k*+1 holes, at least one…

…is *empty*

Pigeonhole Principle



What algorithm can we use?

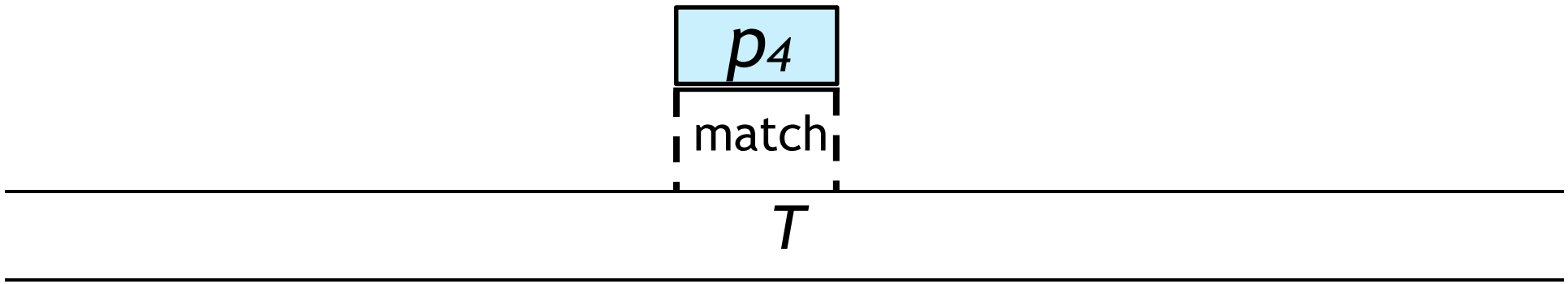
Any exact matching algorithm

If we have a k-mer index, we can use that

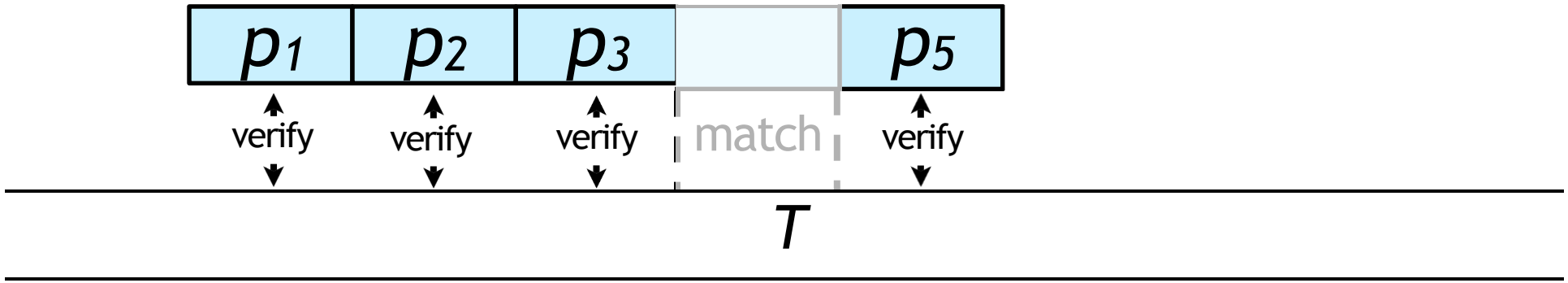
Naive exact matching

Boyer-Moore

Pigeonhole Principle

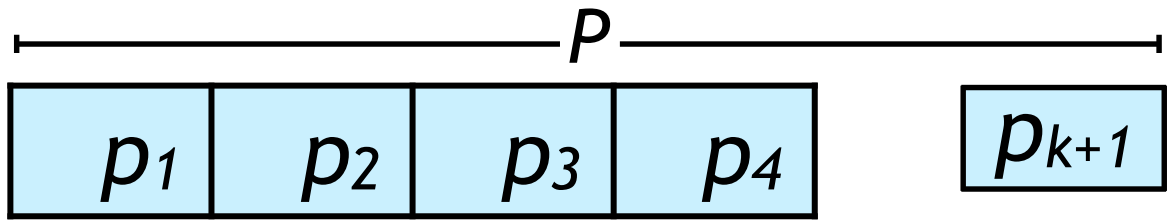


Pigeonhole Principle



For Hamming distance, verification is essentially just the inner loop of **naive_approx_hamming** from before

Pigeonhole Principle



Advantages

Reuse favorite exact matching algos; fast and easy

Flexible; works for Hamming and edit distance*

Disadvantages

Large *k* yields small partitions matching many times by chance; lots of verification work

k+1 exact matching problems, one per partition

* we don't know how to do edit distance verification yet

Pigeonhole Principle

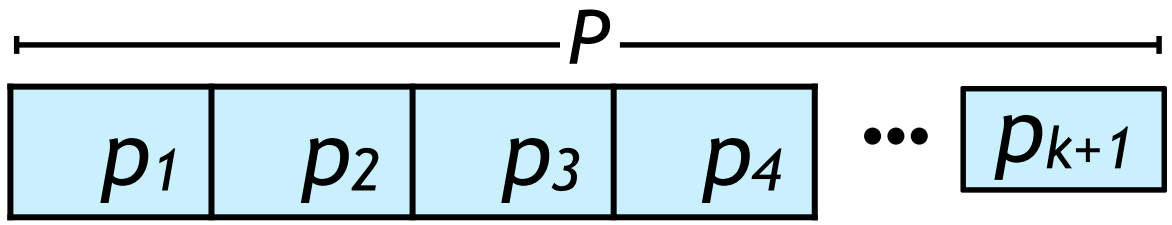
Implementation of pigeonhole principle with Boyer-Moore as exact matching algorithm:
http://j.mp/CG_ApproxBM

	Boyer-Moore, exact			Boyer-Moore, ≤1 mismatch with pigeonhole			Boyer-Moore, ≤2 mismatches with pigeonhole		
	# character comparisons	wall clock time	# matches	# character comparisons	wall clock time	# matches	# character comparisons	wall clock time	# matches
P: "tomorrow" **T**: Shakespeare's complete works	786 K	1.91s	17	3.05 M	7.73 s	24	6.98 M	16.83 s	382
P: 50 nt string from Alu repeat* **T**: Human reference (hg19) chromosome 1	32.5 M	67.21 s	336	107 M	209 s	1,045	171 M	328 s	2,798

* GCGCGGTGGCTCACGCCTGTAATCCCAGCACTTTGGGAGGCCGAGGCGGG

Generalizing pigeonhole, part 1

If P occurs in T with up to k edits, then at least one of $p_1, p_2, \ldots, p_{k+1}$ must appear with 0 edits



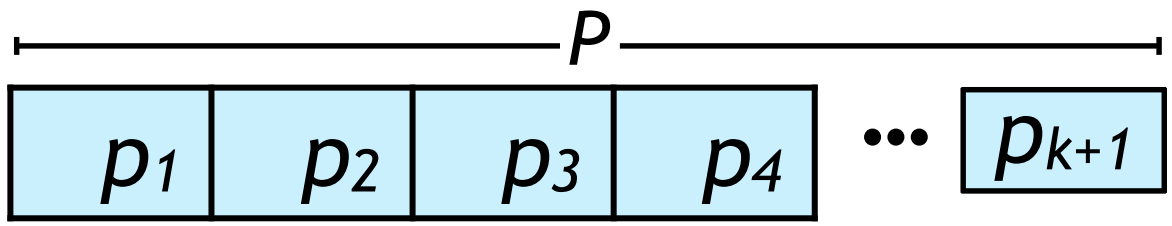
But doesn't *have to* be "at least one of" ...

what would we have to change for "at least two of"?

If P occurs in T with up to k edits, then at least two of _____ must appear with 0 edits

Generalizing pigeonhole, part 1

If P occurs in T with up to k edits, then at least one of $p_1, p_2, \ldots, p_{k+1}$ must appear with 0 edits



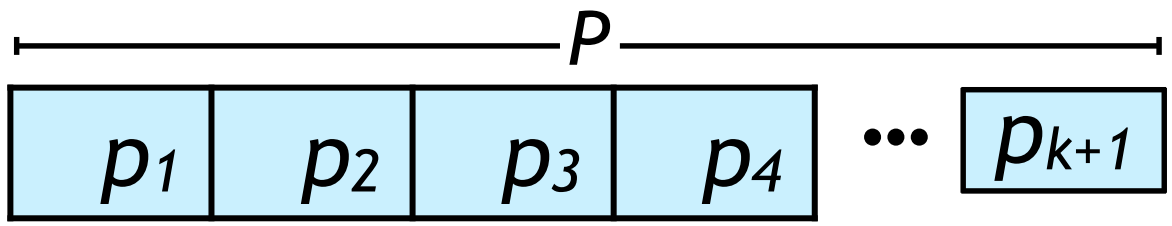
But doesn't *have to* be "at least one of" ...

what would we have to change for "at least two of"?

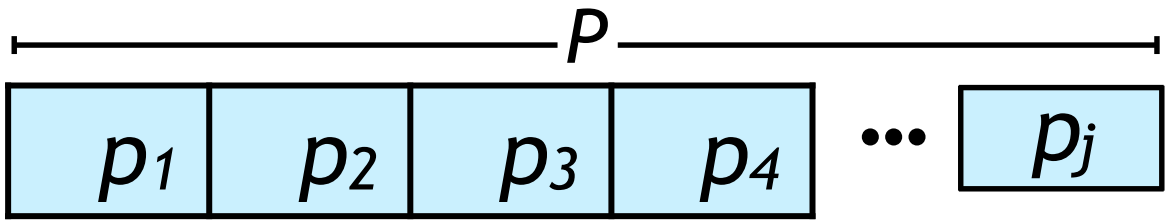
If P occurs in T with up to k edits, then at least two of $p_1, p_2, \ldots, p_{k+2}$ must appear with 0 edits

Generalizing pigeonhole, part 2

If P occurs in T with up to k edits, then at least one of $p_1, p_2, \ldots, p_{k+1}$ must appear with 0 edits

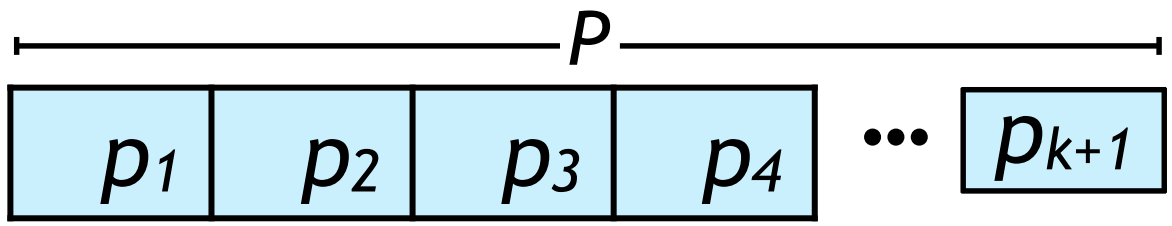


Let $p_1, p_2, \ldots, p_j$ be a partitioning of P. If P occurs with up to k edits, then at least one of $p_1, p_2, \ldots, p_j$ must occur with ≤ ??? edits.

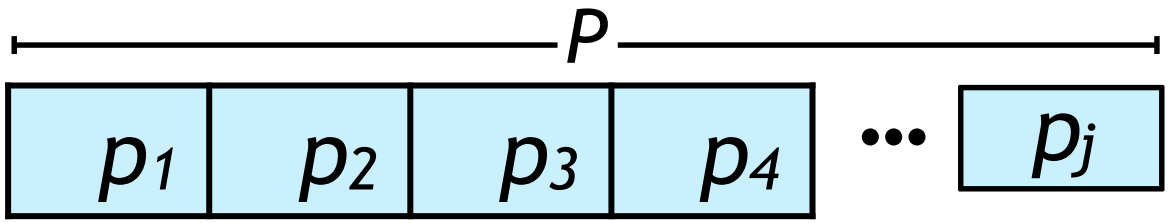


Generalizing pigeonhole, part 2

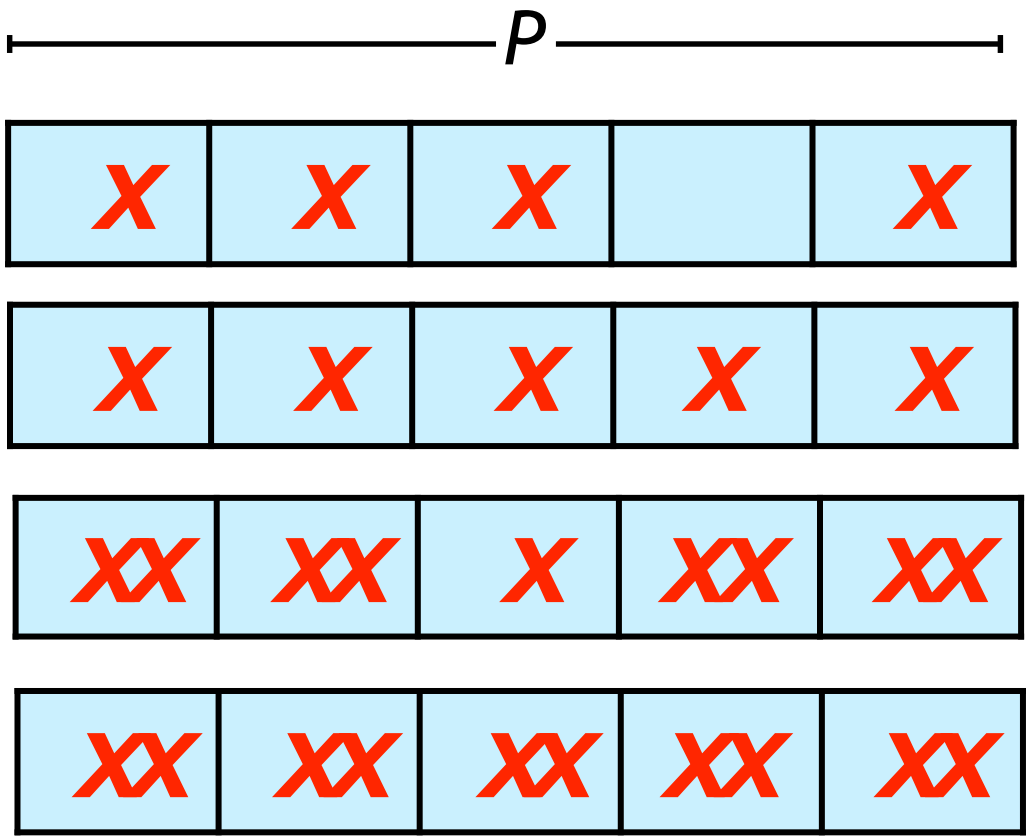
If P occurs in T with up to k edits, then at least one of $p_1, p_2, \ldots, p_{k+1}$ must appear with 0 edits



Let $p_1, p_2, \ldots, p_j$ be a partitioning of P. If P occurs with up to k edits, then at least one of $p_1, p_2, \ldots, p_j$ must occur with $\leq$ *floor*(k / j) edits.



Generalizing pigeonhole, part 2



At least one of $p_1, p_2, \ldots, p_5$ occurs with…

k = 4 edits ≤0 edits

k = 5 edits ≤1 edits

k = 9 edits ≤1 edits

k = 10 edits ≤2 edits

etc

Generalizing pigeonhole, part 2

General

Pigeonhole principle

If P occurs in T with up to k edits, then at least one of $p_1, p_2, \ldots, p_j$ must appear with $floor(k / j)$ edits

Specific

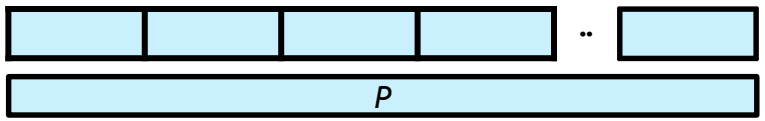
Pigeonhole principle with $j = k + 1$

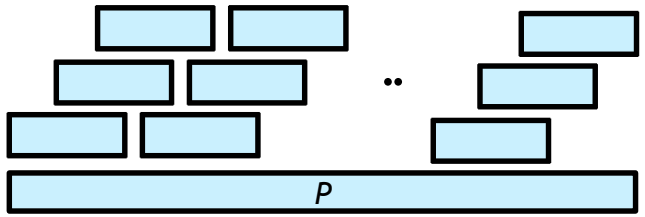
If P occurs in T with up to k edits, then at least one of $p_1, p_2, \ldots, p_{k+1}$ must appear with 0 edits

- Let $j = k + 1$
- *Why?*
- Smallest value s.t. $floor(k / j) = 0$
- *Why make $floor(k / j) = 0$?*
- So we can use exact matching
- *Why is smaller j good?*
- Yields fewer, longer partitions
- *Why are long partitions good?*
- Makes exact-matching filter more specific, minimizing # candidates

Approximate matching principles

	Non-overlapping substrings	Overlapping substrings
General	*Pigeonhole principle* $p_1, p_2, ..., p_j$ is a partitioning of P. If P occurs with $\leq k$ edits, at least one partition matches with $\leq floor(k/j)$ edits.	*q-gram lemma* If P occurs with $\leq k$ edits, alignment contains t exact matches of length q, where $t \geq n - q + 1 - kq$
Specific	*Pigeonhole principle with $j = k + 1$* $p_1, p_2, ..., p_{k+1}$ is a partitioning of P. If P occurrs in T with $\leq k$ edits, at least one partition matches exactly.	*q-gram lemma with $t = 1$* If P occurs with $\leq k$ edits, alignment contains an exact match of length q where $q \geq floor(n/(k+1))$

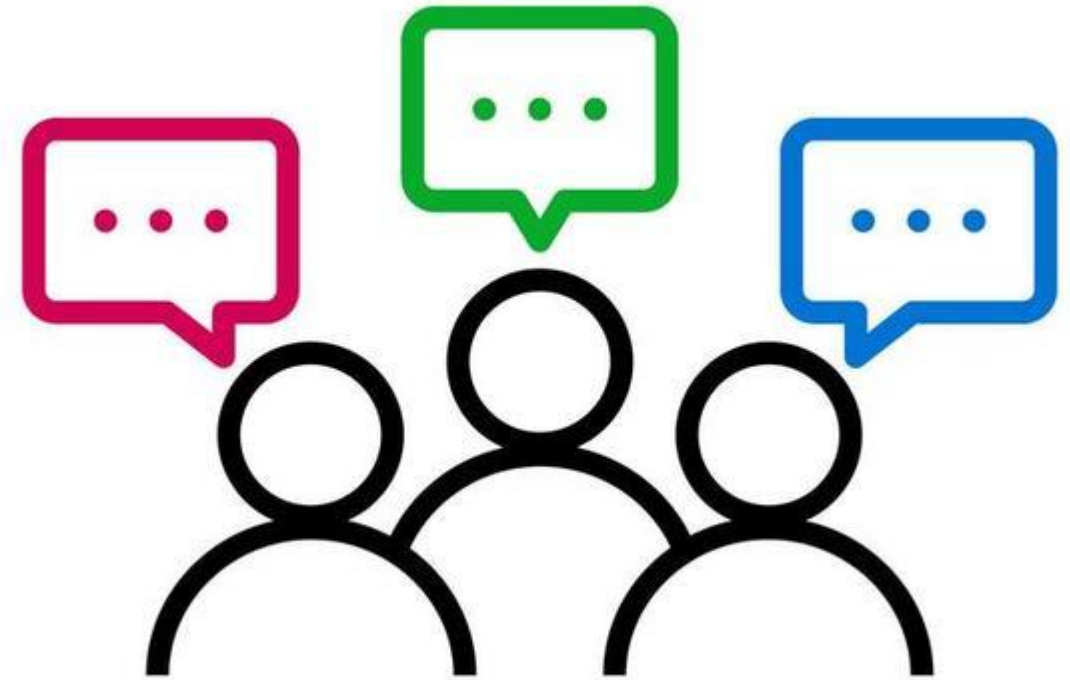




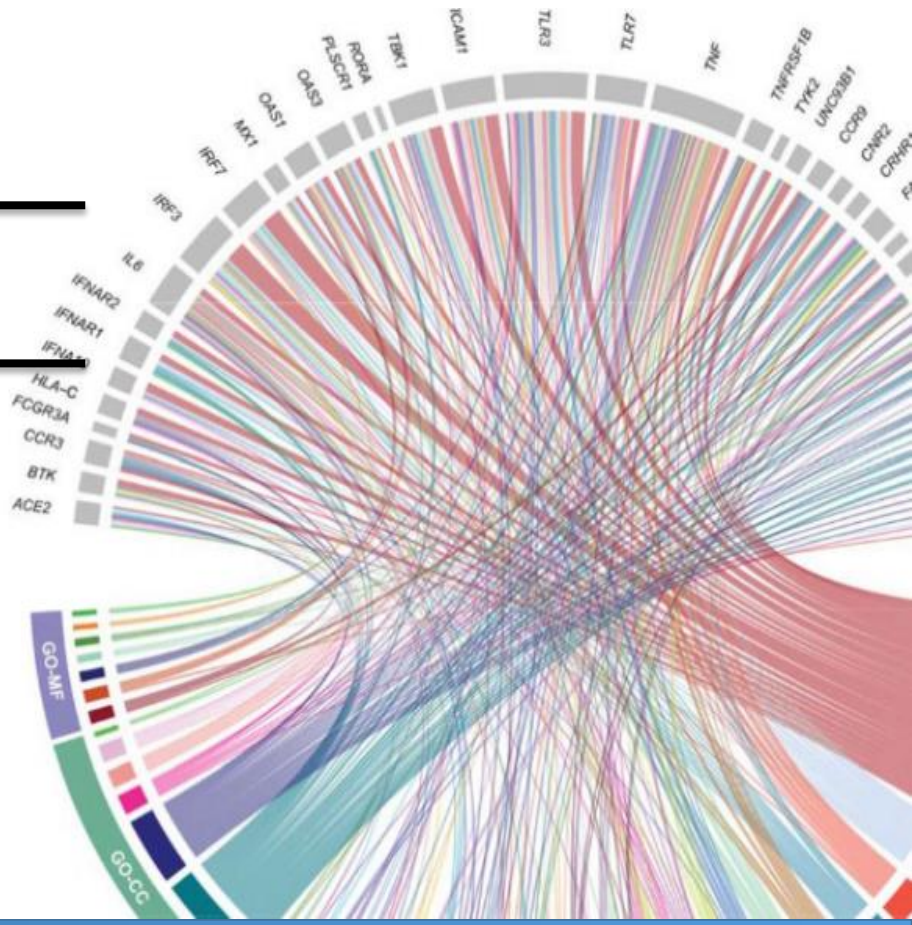
Exercises

1. Indexed Approximate String Matching (using factors)

- Improve the kmer-hash based program to exploit factor filters and find all matches in the reference (chr1.fa) that match a given input-sequence with less than m mismatches.



Questions


ICAM1
TLR3
TLR7
TNF
TNFRSF1B
TYK2
UNC93B1
CCR9
CNR2
TBK1
RORA
PLSCR1
OAS3
OAS1
MX1
IRF7
IRF3
IL6
IFNAR2
IFNAR1
HLA-C
FCGR3A
CCR3
BTK
ACE2
GO-MF
GO-CC