Approximate matching

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Read alignment requires approximate matching

Read

CTCAAACTCCTGACCTTTGGTGATCCACCCGCCTNGGCCTTC

Reference

Sequence differences occur because of...

1. Sequencing error
2. Natural variation

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Approximate string matching

Looking for places where a *P* matches *T* with up to a certain number of mismatches or edits. Each such place is an *approximate match*.

A *mismatch* is a single-character substitution:

```
T: GGAAAAAAGAGGTAGCGGCGTTTAACAGTAG
                |||   |||||||
P:              GTAACGGCG
```

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

```
T: GGAAAAAAGAGGTAGCGGCGTTTAACAGTAG
                |||   |||||||
P:              GTAACGGCG

                        Gap in T
                        ↙
T: GGAAAAAAGAGGTAGC-GCGTTTAACAGTAG
                |||||   |||||||
P:              GTAGCGGCG

T: GGAAAAAAGAGGTAGCGGCGTTTAACAGTAG
                ||   |||||||
P:              GT-GCGGCG

Gap in P
↗
```

Hamming and edit distance

For two same-length strings *X* and *Y*, *hamming distance* is the minimum number of single-character substitutions needed to turn one into the other:

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

Hamming distance = 3

Edit distance (*Levenshtein distance*): minimum number of *edits* required 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

Adapting the naive algorithm to do approximate string matching within configurable Hamming distance:

```
def naiveApproximate(p, t, maxHammingDistance=1):
    occurrences = []
    for i in xrange(0, len(t) - len(p) + 1): # for all alignments
        nmm = 0
        for j in xrange(0, len(p)):          # for all characters
            if t[i+j] != p[j]:               # does it match?
                nmm += 1                     # mismatch
                if nmm > maxHammingDistance:
                    break                    # exceeded maximum distance
        if nmm <= maxHammingDistance:
            # approximate match; return pair where first element is the
            # offset of the match and second is the Hamming distance
            occurrences.append((i, nmm))
    return occurrences
```

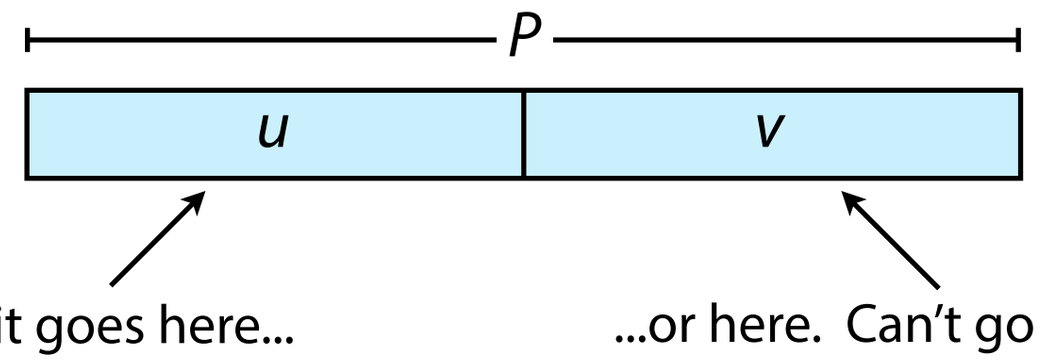
Instead of stopping upon first mismatch, stop when maximum distance is exceeded

Python example: http://bit.ly/CG_NaiveApprox

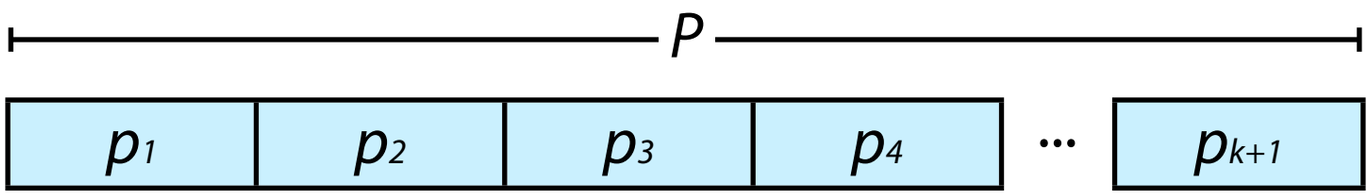
Approximate string matching

How to make Boyer-Moore and index-assisted exact matching approximate?

Helpful fact: Split *P* into non-empty non-overlapping substrings *u* and *v*. If *P* occurrs in *T* with 1 edit, either *u* or *v* must match exactly.



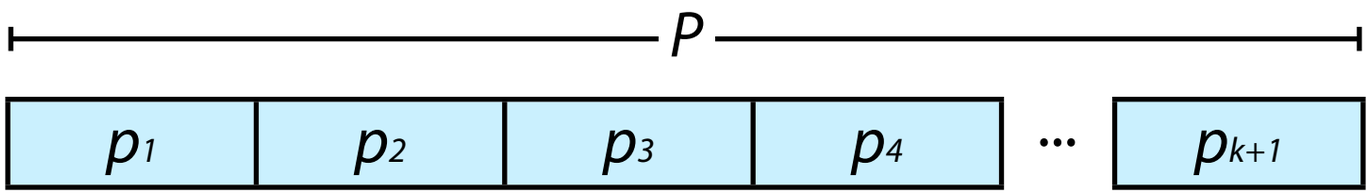
More generally: Let $p_1, p_2, ..., p_{k+1}$ be a partitioning of *P* into *k*+1 non-overlapping non-empty substrings. If *P* occurrs in *T* with up to *k* edits, then at least one of $p_1, p_2, ..., p_{k+1}$ must match exactly.



≤ *k* edits can affect as many as *k* of these, but not all

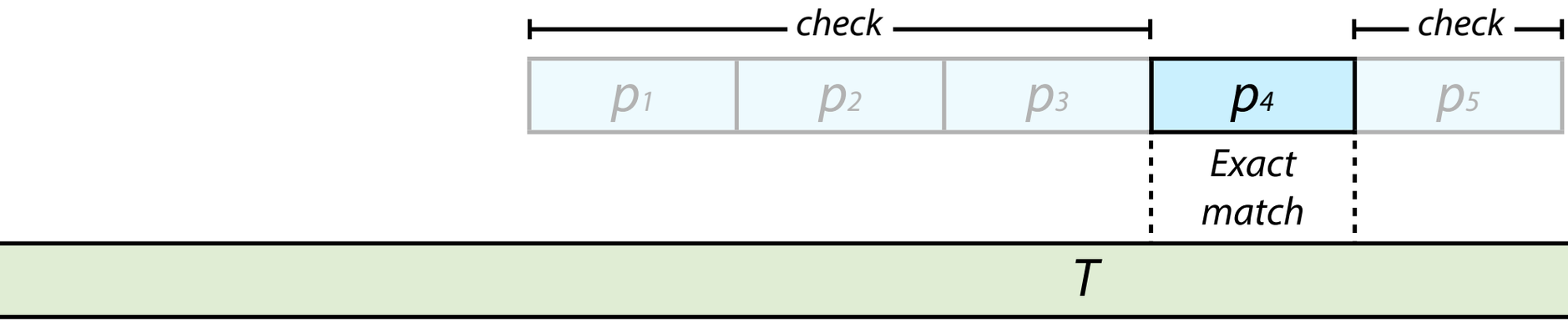
Approximate string matching

These rules provides a bridge from the exact-matching methods we've studied so far, and approximate string matching.



≤ *k* edits can overlap as many as *k* of these, but not all

Use an exact matching algorithm to find exact matches for p_1, p_2, ..., p_{k+1}.
Look for a longer approximate match in the vicinity of the exact match.



Approximate string matching

```
def bmApproximate(p, t, k, alph="ACGT"):
    """ Use the pigeonhole principle together with Boyer-Moore to find
        approximate matches with up to a specified number of mismatches. """
    if len(p) < k+1:
        raise RuntimeError("Pattern too short (%d) for given k (%d)" % (len(p), k))
    ps = partition(p, k+1) # split p into list of k+1 non-empty, non-overlapping substrings
    off = 0                # offset into p of current partition
    occurrences = set()    # note we might see the same occurrence >1 time
    for pi in ps:          # for each partition
        bm_prep = BMPreprocessing(pi, alph=alph) # BM preprocess the partition
        for hit in bm_prep.match(t)[0]:
            if hit - off < 0: continue # pattern falls off left end of T?
            if hit + len(p) - off > len(t): continue # falls off right end?
            # Count mismatches to left and right of the matching partition
            nmm = 0
            for i in range(0, off) + range(off+len(pi), len(p)):
                if t[hit-off+i] != p[i]:
                    nmm += 1
                    if nmm > k: break # exceeded maximum # mismatches
            if nmm <= k:
                occurrences.add(hit-off) # approximate match
        off += len(pi) # Update offset of current partition
    return sorted(list(occurrences))
```

Full example: http://bit.ly/CG_BoyerMooreApprox

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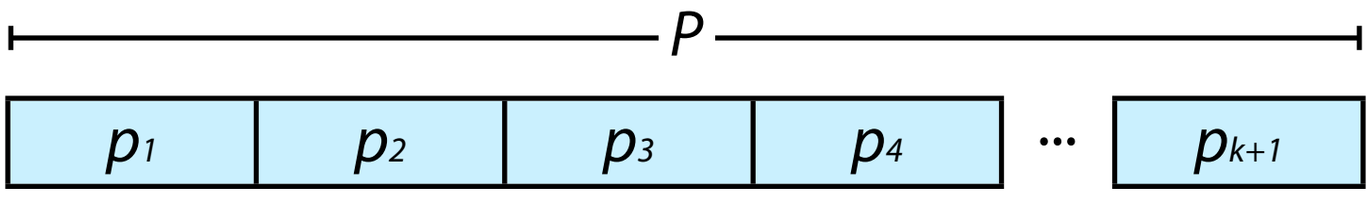
Approximate Boyer-Moore performance

	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

Approximate string matching: more principles

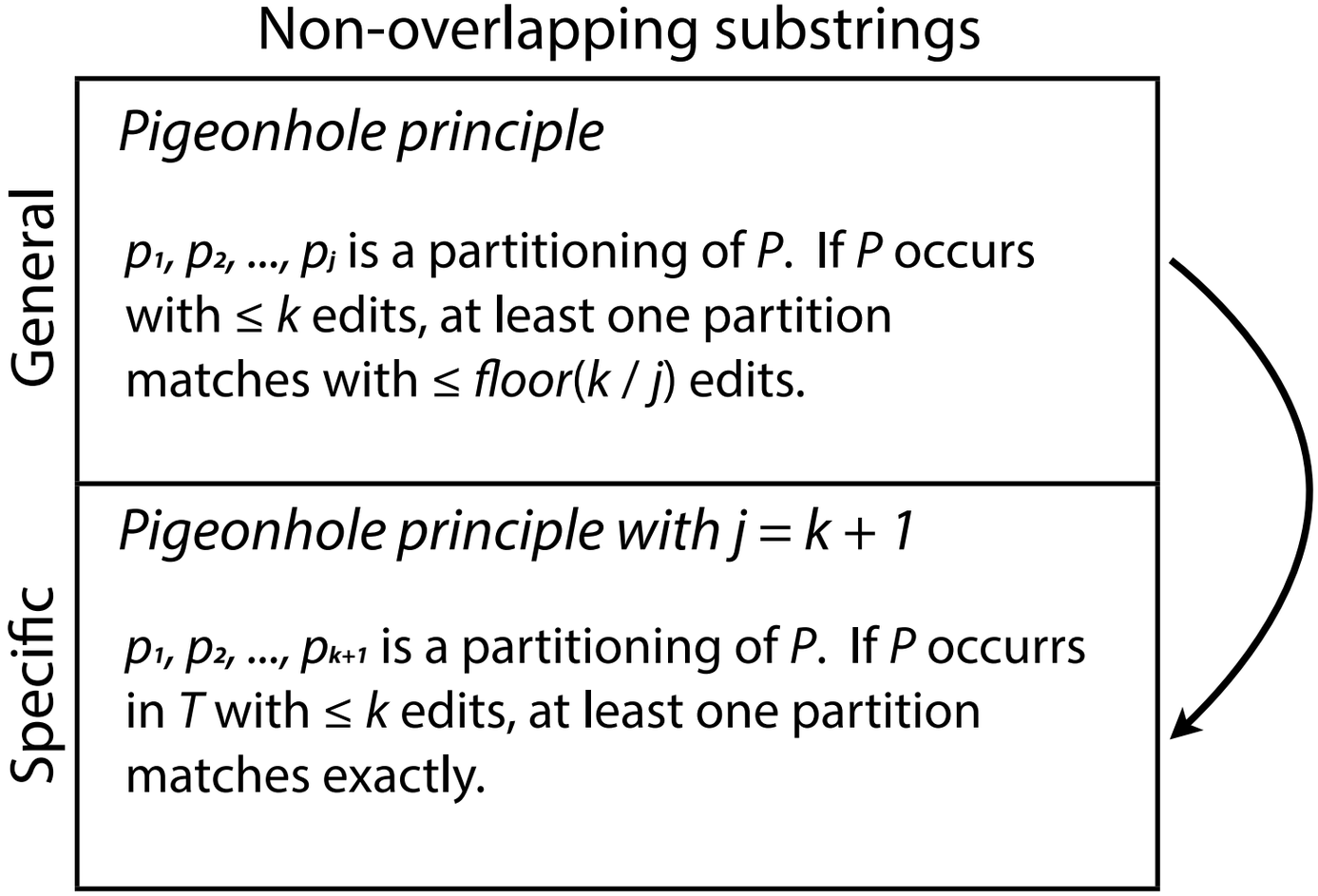
Let p_1, p_2, ..., p_{k+1} be a partitioning of P into k+1 non-overlapping non-empty substrings. If P occurrs in T with up to k edits, then at least one of p_1, p_2, ..., p_{k+1} must match exactly.



New principle:

Let p_1, p_2, ..., p_j be a partitioning of P into j non-overlapping non-empty substrings. If P occurs with up to k edits, then at least one of p_1, p_2, ..., p_j must occur with ≤ *floor*(k / j) edits.

Review: approximate matching principles



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?

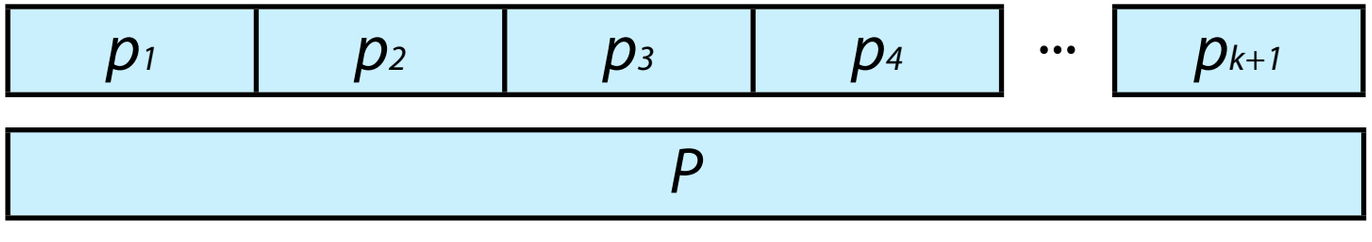
Yields fewer, longer partitions

Why are long partitions good?

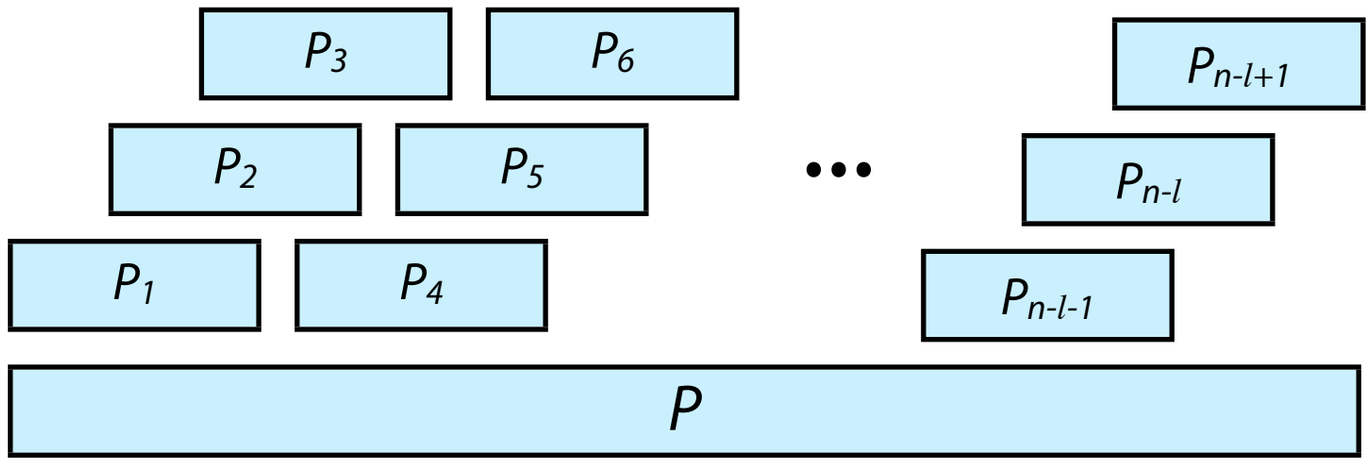
Makes exact-matching filter more specific, minimizing # candidates

Approximate string matching: more principles

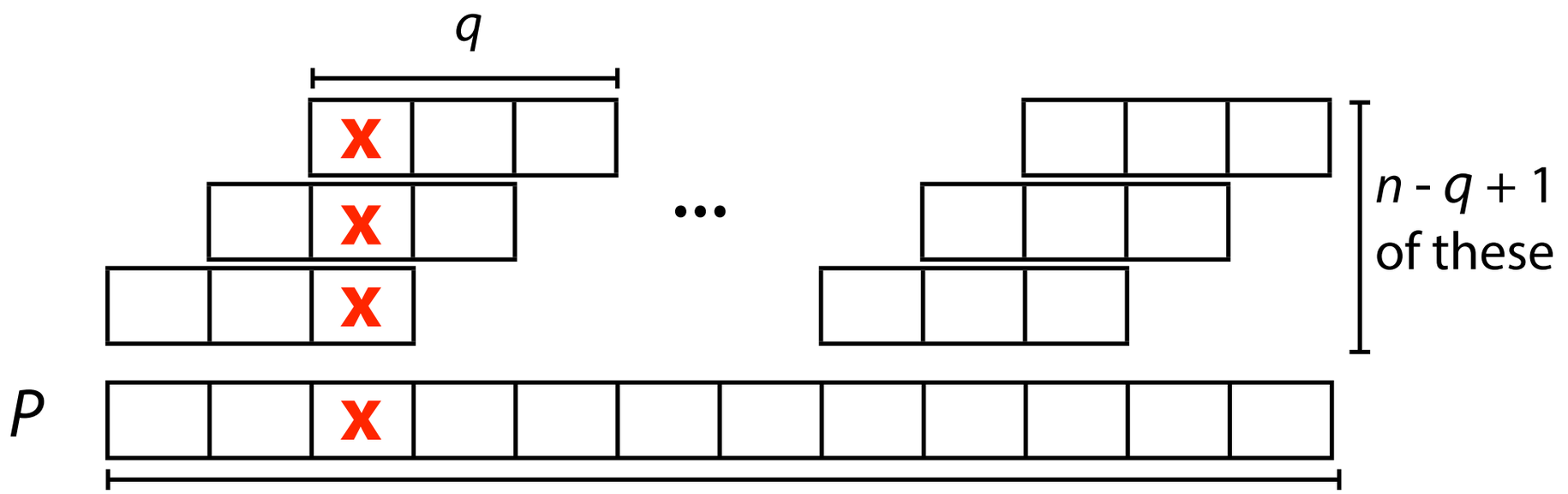
We partitioned *P* into non-overlapping substrings



Consider overlapping substrings



Approximate string matching: more principles



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

Worst case: 1 edit to *P* changes up to *q* substrings

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: more principles

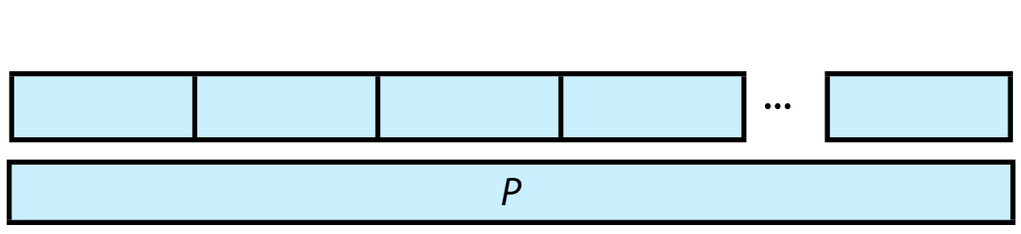
If *P* occurs in *T* with up to *k* edits, alignment contains an exact match of length *q,* where $q \geq floor(n / (k + 1))$

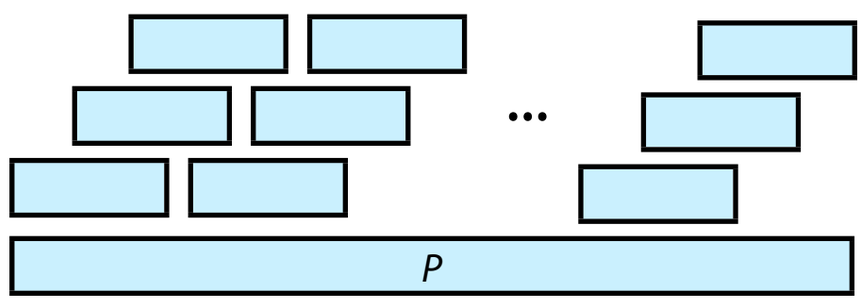
Derived by solving this for *q*: $n - q + 1 - kq \geq 1$

Exact matching filter: find matches of length $floor(n / (k + 1))$ between *T* and *any* substring of *P*. Check vicinity for full match.

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 $q \geq floor(n / (k + 1))$



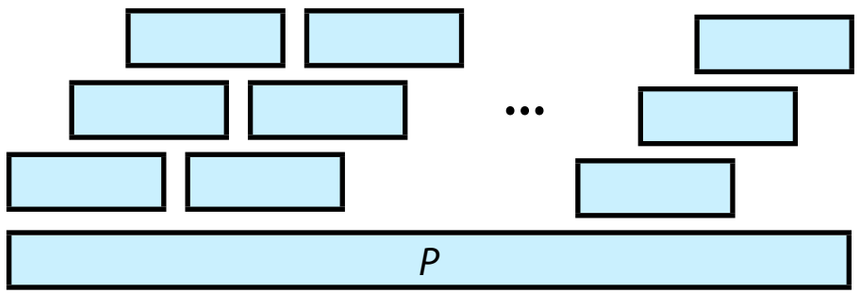


Sensitivity

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 often much speedier & still acceptably sensitive (e.g. BLAST, BLAT, Bowtie).



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