Error Tolerant Pattern Matching II

Algorithms for Sequence Analysis

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Summer 2021

Overview

Previous Lecture

- Pattern Matching with respect to edit distance
- **Semiglobal** Alignment:
  Compare one full string (pattern) against substrings of a longer string (text)
- Basic algorithm
- Ukkonen's speed-up
- Ideas of Myers' bit vector algorithm

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Today's Lecture

- Adapting NFAs (and Shift-And) to error tolerant search
- Combining NFAs and full text indexing (FM index)
- Four Russians' Method

Reminder: Error Tolerant Pattern Matching

Problem Definition

- For two strings $P, T \in \Sigma^*$, find **approximate occurrences** of P in T.
- **Formally:** Find **intervals** $[i, j]$ of T such that the **edit distance** between P and $T[i \dots j]$ is below a given threshold k.

Variants

- **Decision Problem:** Is there an interval ... ?
- **Counting Problem:** How many intervals ... ?
- **Enumeration Problem:** List all intervals ....
- **Optimization Problem:** Find an interval $[i, j]$ with the smallest edit distance between P and $T[i \dots j]$ among all (no threshold k given).

Reminder: NFA for the Exact Pattern Matching Problem

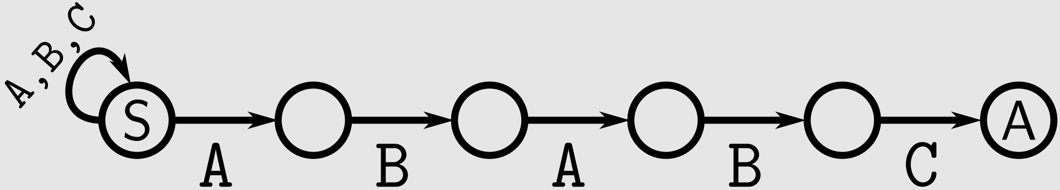
Goal

For given pattern $P \in \Sigma^*$, construct NFA that recognizes all strings $\Sigma^* P$.

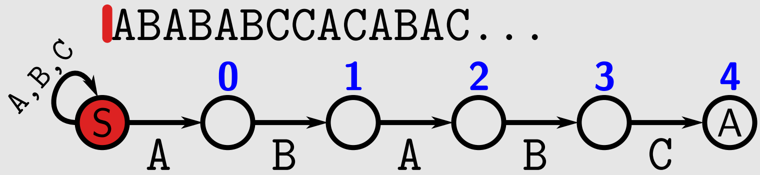
Approach

- "Linear chain" of states
- Start state remains always active

Example: $\Sigma = \{\mathtt{A}, \mathtt{B}, \mathtt{C}\}$ and $P = \mathtt{ABABC}$



Reminder: The Shift-And Algorithm



D:	0	0	0	0	0
$mask(\mathtt{A})$:	1	0	1	0	0
$mask(\mathtt{B})$:	0	1	0	1	0
$mask(\mathtt{C})$:	0	0	0	0	1

$$D \leftarrow \big((D \ll 1)|1\big)\ \&\ \mathrm{mask}[c]$$

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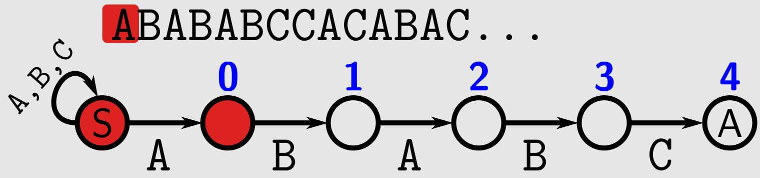

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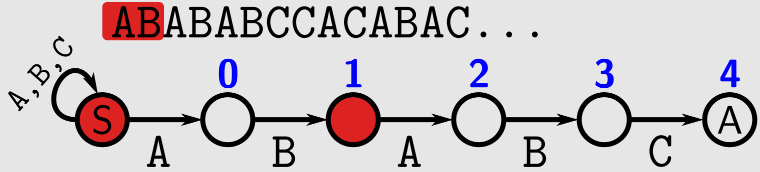

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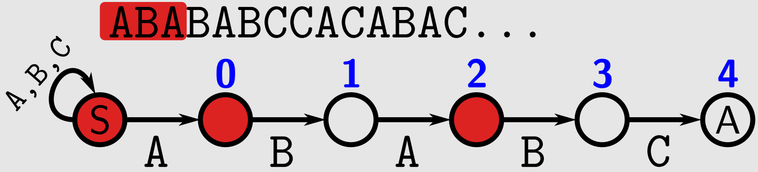

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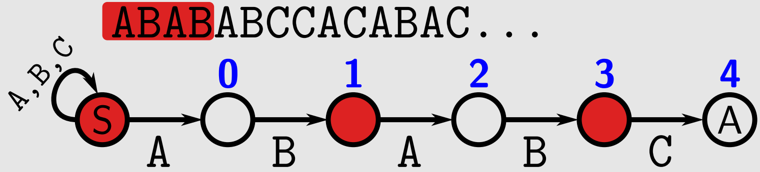

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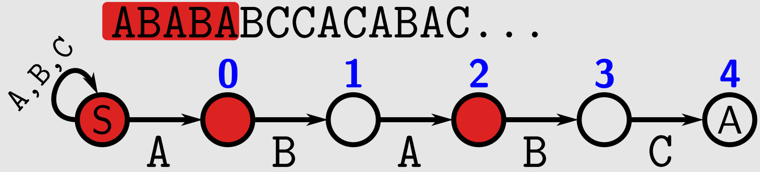

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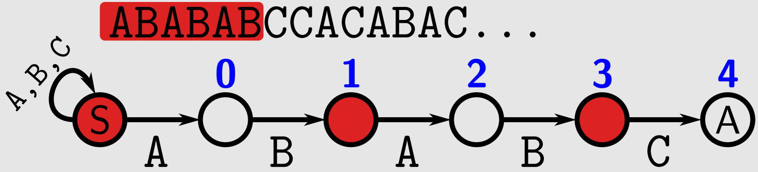

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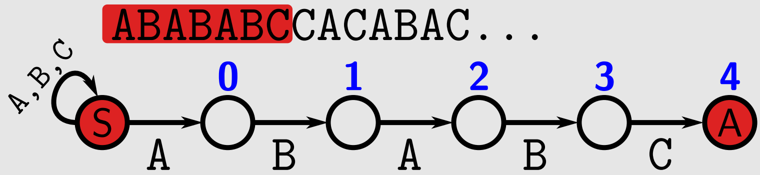

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Extension to Error Tolerant Pattern Search

Idea

- Start from NFA for exact pattern search
- Add k additional "rows" account for up to k errors
- State space: $Q = \{0, \dots, k\} \times \{-1, \dots, m-1\}$ for pattern P with $|P| = m$.

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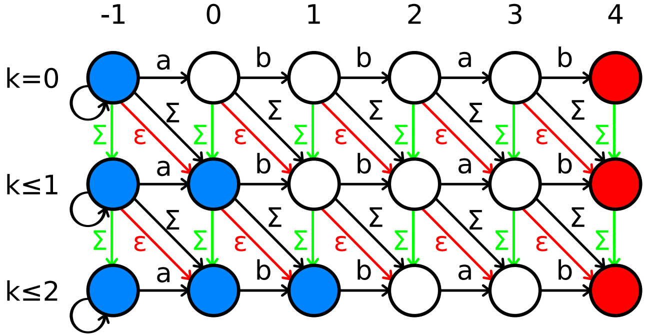

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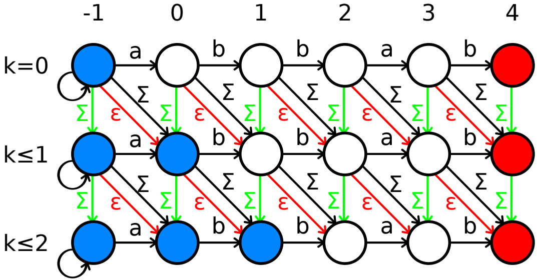
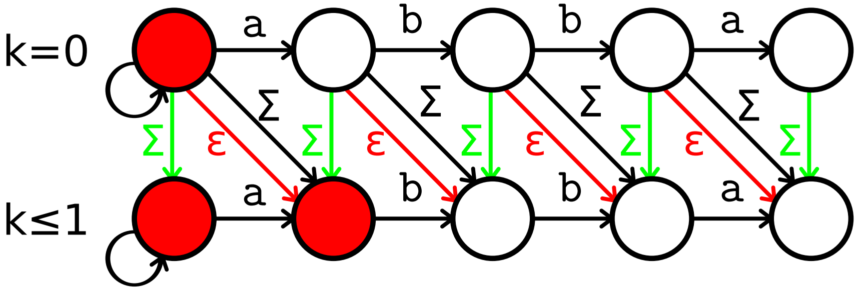


- NFA for $P = \texttt{abbab}$ with edit distance up to 2 and $\Sigma = \{a, b\}$
- blue states: start states, red states: accepting states
- green vertical edges: **insertions in** P
- red diagonal edges: ε edges for **deletions in** P
- black diagonal edges: Σ edges for **mismatches in** P

Example

`abcabba`



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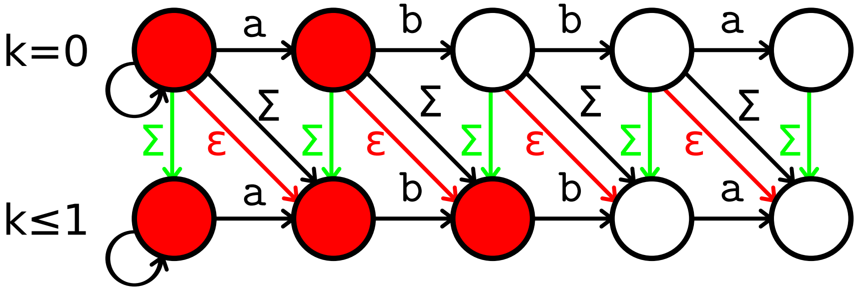

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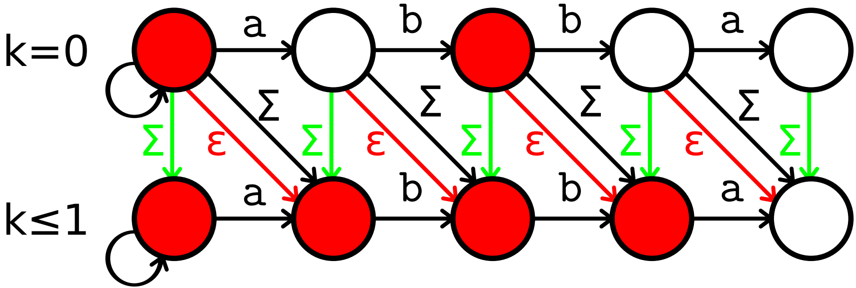

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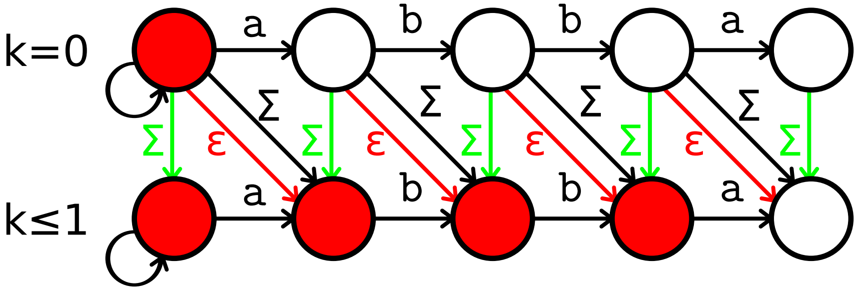

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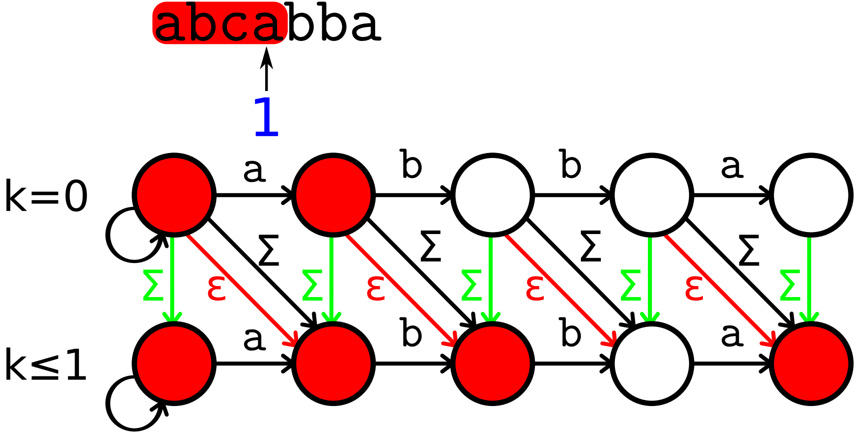

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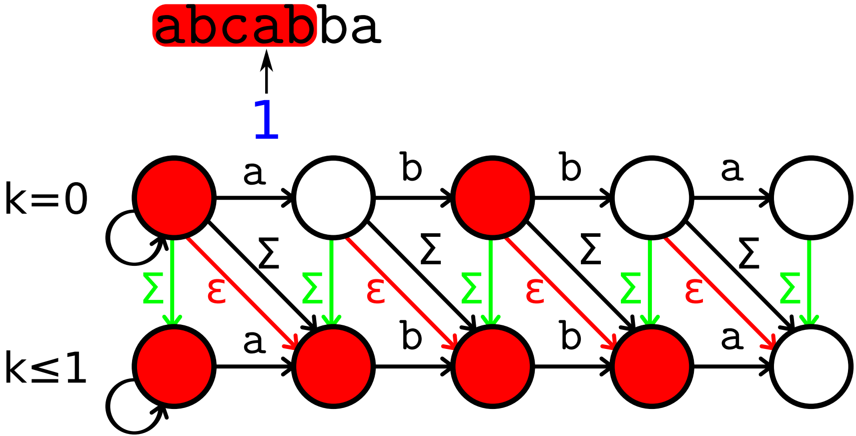

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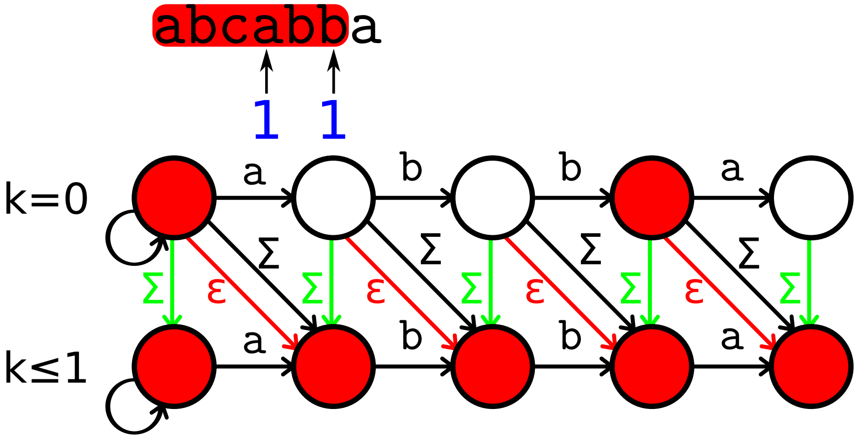

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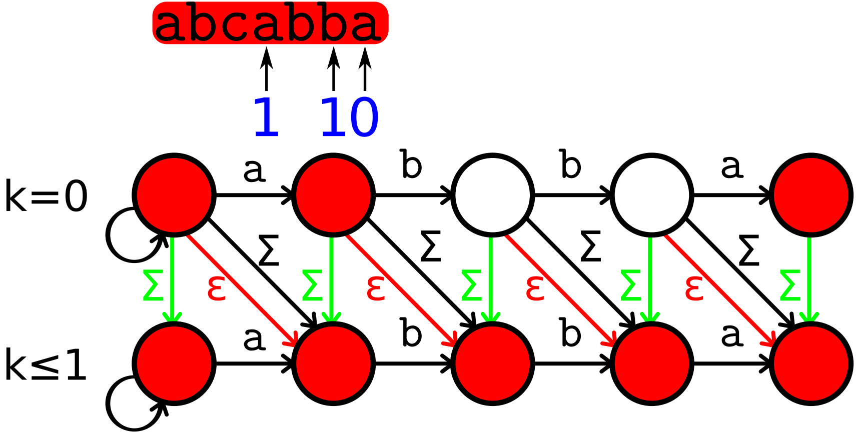
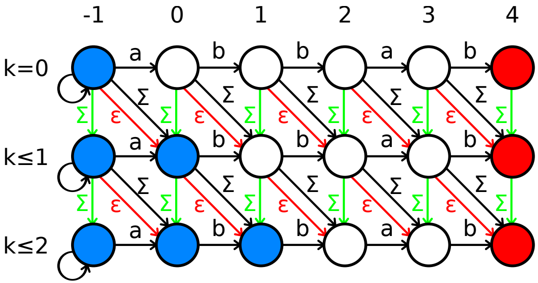


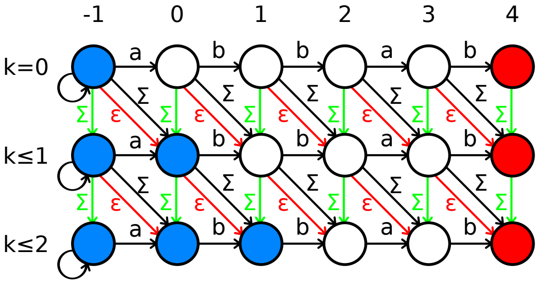
Bit-Parallel Implementation



$$A_0 \leftarrow (A_0^{(\text{old})} \ll 1|1)\ \&\ mask[c]$$

$$A_i \leftarrow ((A_i^{(\text{old})} \ll 1|1)\ \&\ mask[c])\ |\ \underbrace{\left(A_{i-1}^{(\text{old})}\right)}_{\text{insertions}}\ |\ \underbrace{\left(A_{i-1}^{(\text{old})} \ll 1\right)}_{\text{mismatches}}\ |\ \underbrace{\left(A_{i-1} \ll 1\right)}_{\text{deletions}} \text{ for } 0 < i \leq k.$$

Observations



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- Needs a loop from 0 to k: only efficient for small k.
- Flexible: use generalized strings, gaps of bounded length, optional characters...

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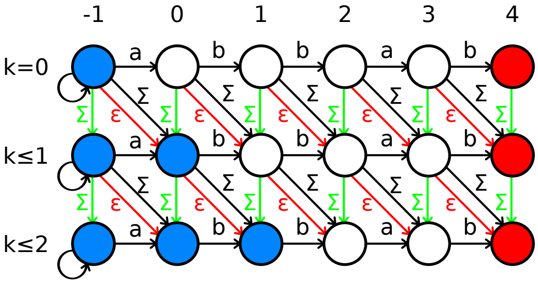

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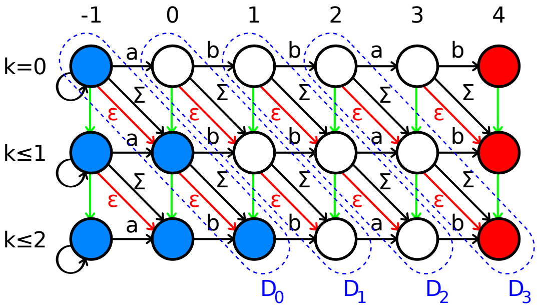
- Needs a loop from 0 to k: only efficient for small k.
- Flexible: use generalized strings, gaps of bounded length, optional characters...
- One more trick: Remove loop over k for small patterns, less flexible

Diagonal Encoding

- Instead of encoding the rows of the NFA, encode the **diagonals** in **one** bit vector.
- All states in diagonals together plus separator bits must fit into 64 bits.
- Can do update in time independent of k then (no loop).
- Loss of flexibility; details omitted here.



Error Tolerant Backward Search

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So far

- Online algorithms, no full-text index: all have $O(n)$ time factor

Now

- Assume that we have a full-text index, e.g., FM index.
- Achieves running times independent of $|T| = n$ for exact pattern search.
- Generalization for error tolerant pattern search?

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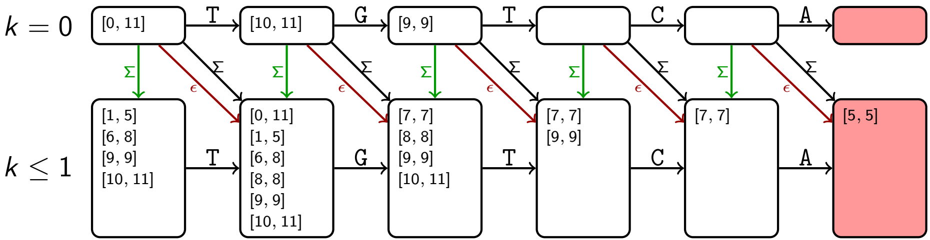
Idea

- Hybrid approach between backward search and NFA.
- NFA states do not contain bits ("activity"), but sets of suffix array intervals.
- Intervals evolve along edges according to backward search.

Example: Error Tolerant Backward Search

$T = \texttt{AAAACGTACCT\$}$, $\quad P = \texttt{ACTGT}$, $\quad \Sigma = \{\texttt{A}, \texttt{C}, \texttt{G}, \texttt{T}\}$:



- Green edges: insertions
- Red edges (ε): deletions
- Black edges: matches (horizontal) and mismatches (diagonal)
- Note: numbers for illustration only, not necessarily correct.

Formal Description: Error Tolerant Backward Search

- $(k+1) \times (m+1)$ matrix $M = (M[0 \dots k,\ 0 \dots m])$
- $M[i,j]$: set of intervals $[L,R]$, such that
  the length-j suffix of P occurs with $\leq i$ edit operations at $\mathtt{pos}[r]$ for all $r \in [L,R]$.
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  4. Process substitutions: the same $[L_s^+, R_s^+]$ are also inserted into $M[i+1, j+1]$.
- Matches are found whenever an accepting state contains an interval.
- Optimization: Merge intervals before processing each node

The Four Russians Method

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Answer

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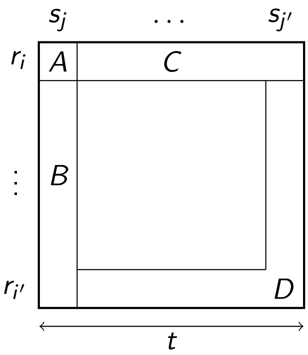
No, not really and not generally.

However...

We can save a log factor by tabulation of all possible sub-matrices.
This is called the **Method of Four Russians** (1970),
according to its inventors Arlazarov, Dinic, Kronrod and Faradzev.

Basic Idea

- Within a submatrix as shown the results D depend only on the inputs A, B, C and on the substrings $r' = r[i \dots i'],\ s' = s[j \dots j']$.
- **Definition:** A t-block is a $t \times t$ submatrix.



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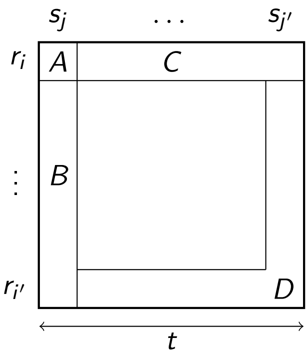
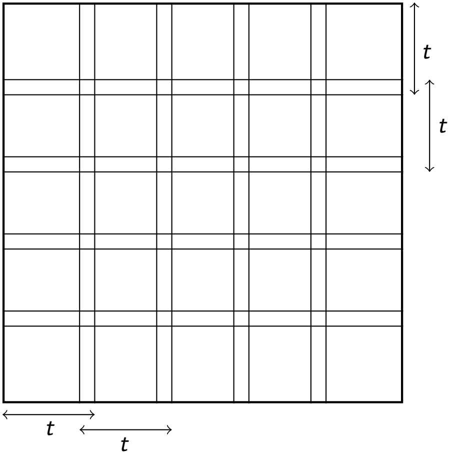
- **Definition:** A t-block is a $t \times t$ submatrix.
- **Idea:** Subdivide matrix into t-blocks. Pre-compute results (D) for all combinations of (A, B, C, r', s').
- Avoid redundancies.



Basic Idea

Subdivide matrix into overlapping t-blocks:



Reminder: Matrix Properties

Let T be a DP matrix satisfying the edit distance recurrence.

Lemma: Vertical Property

The value difference between any two **vertically adjacent** cells is at most 1:
$|T[i,j] - T[i-1,j]| \leq 1$.

Lemma: Horizontal Property

The value difference between any two **horizontally adjacent** cells is at most 1:
$|T[i,j] - T[i,j-1]| \leq 1$.

Lemma: Diagonal Property

The value of **diagonally adjacent** cells is non-decreasing,
and the value difference is at most 1, i.e., $0 \leq T[i,j] - T[i-1,j-1] \leq 1$.

Observation

If the input values (areas A, B, C) in two t-blocks differ by one offset,
and if the substrings are identical,
then the output values (area D) differ by the same offset.

	a	b	b	a
b	5	6	5	4
a	6	6	6	5
b	6	6	6	6
a	7	7	7	6

	a	b	b	a
b	2	3	2	1
a	3	3	3	2
b	3	3	3	3
a	4	4	4	3

Preprocessing

To avoid pre-computing t-blocks for (infinitely) many combinations of A, B, C, we consider A as an offset, and difference vectors δ_B, δ_C:
Let $\delta_B[0] := 0$, and $\delta_B[i] := B[i] - B[i-1]$.
Let $\delta_C[0] := 0$, and $\delta_C[j] := C[j] - C[j-1]$

	a	b	b	a
b	5	6	5	4
a	6			
b	6			
a	7			

$\rightarrow$

	a	b	b	a
b	0	1	-1	-1
a	1			
b	0			
a	1			

$$B = [5, 6, 6, 7] \quad \rightarrow \quad \delta_B = [(0,)1, 0, 1]$$

$$C = [5, 6, 5, 4] \quad \rightarrow \quad \delta_C = [(0,)1, -1, -1]$$

Preprocessing

Running time for pre-computing all blocks

- Because $\delta_B[0] = \delta_C[0] = 0$ and the other δ-values are limited to $\{-1, 0, 1\}$, there are at most $3^{2(t-1)}$ combinations for (δ_B, δ_C).

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- There are $\sigma^{2(t-1)}$ different substring combinations.
- Pre-computing a t-block takes $O((t-1)^2)$ time.

Preprocessing

Running time for pre-computing all blocks

- Because $\delta_B[0] = \delta_C[0] = 0$ and the other δ-values are limited to $\{-1, 0, 1\}$, there are at most $3^{2(t-1)}$ combinations for (δ_B, δ_C).
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Memory requirements

- To store the result (D region) for one block: $O(t)$ bits (difference-encoded)
- Total: $O(n \log n)$ bits, or n integers.

Computation

	-	a	b	b	a	b	a
-							
b							
b							
a							
a							
b							
a							

Computation

1. Initialize row and column 0

$\delta_B =$

$\delta_C =$

$A =$

$D =$

	-	a	b	b	a	b	a
-	0	1	2	3	4	5	6
b	1						
b	2						
a	3						
a	4						
b	5						
a	6						

Computation

1. Initialize row and column 0
2. For all $i < m/t$ and $j < n/t$:

$\delta_B =$

$\delta_C =$

$A = 0$

$D =$

	-	a	b	b	a	b	a
-	0	1	2	3	4	5	6
b	1						
b	2						
a	3						
a	4						
b	5						
a	6						

Computation

1. Initialize row and column 0
2. For all $i < m/t$ and $j < n/t$:
3. Compute δ_B, δ_C from B, C
   (or re-use old difference-encoded D)

$\delta_B = 0, 1, 1, 1$
$\delta_C = 0, 1, 1, 1$
$A = 0$
$D =$

	-	a	b	b	a	b	a
-	0	1	2	3	4	5	6
b	1						
b	2						
a	3						
a	4						
b	5						
a	6						

Computation

1. Initialize row and column 0
2. For all $i < m/t$ and $j < n/t$:
3. Compute δ_B, δ_C from B, C (or re-use old difference-encoded D)
4. Lookup: $D = F[\delta_B, \delta_C, r[i' : i''], s[j' : j'']]$.

$\delta_B = 0, 1, 1, 1$
$\delta_C = 0, 1, 1, 1$
$A = 0$
$D = 2, 2, 2, 1, 2$

	-	a	b	b	a	b	a
-	0	1	2	3	4	5	6
b	1						
b	2						
a	3						
a	4						
b	5						
a	6						

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5. Keep track of offset A.

$\delta_B = 0, 1, 1, 1$
$\delta_C = 0, 1, 1, 1$
$A = 0$
$D = 2, 2, 2, 1, 2$

	-	a	b	b	a	b	a
-	0	1	2	3	4	5	6
b	1			2			
b	2			1			
a	3	2	2	2			
a	4						
b	5						
a	6						

Computation

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5.   Keep track of offset A.

$\delta_B = 0, 1, 1, 1$
$\delta_C = 0, -1, 0, 0$
$A = 3$
$D = 2, 1, 1, 0, 0$

	-	a	b	b	a	b	a
-	0	1	2	3	4	5	6
b	1			2			
b	2			1			
a	3	2	2	2			
a	4			3			
b	5			3			
a	6	5	4	4			

Computation

1. Initialize row and column 0
2. For all $i < m/t$ and $j < n/t$:
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5. Keep track of offset A.

$\delta_B = 0, -1, -1, 1$
$\delta_C = 0, 1, 1, 1$
$A = 3$
$D = -2, -1, 0, 1, 2$

	-	a	b	b	a	b	a
-	0	1	2	3	4	5	6
b	1			2			5
b	2			1			4
a	3	2	2	2	1	2	3
a	4			3			
b	5			3			
a	6	5	4	4			

Computation

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2. For all $i < m/t$ and $j < n/t$:
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5. Keep track of offset A.

$\delta_B = 0, 1, 0, 1$
$\delta_C = 0, -1, 1, 1$
$A = 2$
$D = 1, 1, 0, 1, 0$

	-	a	b	b	a	b	a
-	0	1	2	3	4	5	6
b	1			2			5
b	2			1			4
a	3	2	2	2	1	2	3
a	4			3			2
b	5			3			3
a	6	5	4	4	3	3	2

Running Time for Error Tolerant Pattern Search

Time for one t-block

- Compute differences: $O(t)$
- Look-up $F[q]$ in big table: $O(t)$ for computing index q
- Keeping track of offset: $O(t)$
- Total time for each block: $O(t)$

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Total time

- Number of t-blocks: mn/t^2
- Total time: $O(t \cdot nm/t^2) = O(nm/t) = O(nm/\log n)$

Summary: Four Russians Method

Running Times

- With the Four-Russians trick (difference coding, pre-computation of small blocks), one can compute the edit distance or do pattern search in sub-quadratic time.
- Pre-computation (all possible blocks): $O\left(n\,(\log n)^2\right)$ time
- Computation for two strings: $O(nm/\log n)$ time

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Practicality

- Because of the high base in the logarithm $(t := 1 + (\log_{3\sigma} n)/2)$, the method is only practical for large $n \geq 10\,000$, especially for small alphabets (DNA: $\sigma = 4$).
- For larger alphabets, much memory is needed.
- Therefore, the Four Russians Method is rarely used in practice.

Comparison of Running Times

algorithm	time	advantages	disadvantages
Basic	$O(mn)$	simple	slow
Ukkonen	$O(kn)$ expected	simple	
Myers	$O((m/w)n)$	fast for high k	unintuitive
NFA	$O(k(m/w)n)$	fast for small m or k	slow for large k
4 Russians	$O(mn/\log n)$	nice idea	only faster for large n
NFA-FM	(*)	independent of n	exponential in $\|\Sigma\|$, m, k

(*) NFA-FM time can be shown to be $O(\sqrt{k}\,(1+\sqrt{2})^{2k}\,3^{m-k}|\Sigma|^k)$ for $k \leq m$.

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Notes

- w ist the register size, typically 64 bits.
- Alignments can only be easily derived from the Basic and Ukkonen algorithms.

Summary

Today

- NFA for error tolerant pattern matching
- error tolerant pattern matching with FM index (via interval NFA)
- Four Russians' method: tabulation of small submatrices
- Comparison of algorithms

Possible Exam Questions

- Explain how the Shift-And algorithm can be adjusted to solve the approximate pattern matching problem.
- Explain the semantics of the states in the corresponding NFA.
- Explain the meaning of the different types of edges.
- How many states are always active for a NFA that allows k mismatches?
- How exactly does the bit-parallel update of the active state matrix A work?
- How can backward search be applied to error tolerant search?
- Explain the idea of the Four Russians Technique.
- Why is the block size chosen as $t := 1 + (\log_{3\sigma} n)/2$ in the Four Russians Method?