Session 9 –Theory and Exercises

Read Alignment I: The FM Index

ESCI upf.
School of International Studies
BelongBecome

Date: 12/02/2024, 15:00-17:00

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Bachelor's Degree in Bioinformatics
Course 2023-2024
52115 - Algorithms for sequence analysis in Bioinformatics (**ASAB**)

Read

CTCAAACTCCTGACCTTTGGTGATCCACCCGCCTNGGCCTTC

Reference

Sequence differences occur because of...

1. Sequencing error
2. Genetic variation

https://langmead-lab.org/teaching-materials/

What do we need to determine the original genomic location of these reads?

Global Alignment with Respect to the Reads

Local Alignment

Target Sequence

```
5' ACTACTAGATTACTTACGGATCAGGTACTTTAGAGGCTTGCAACCA 3'
             |||| |||||| ||||||||||||||||
Query Sequence 5' TACTCACGGATGAGGTACTTTAGAGGC 3'
```

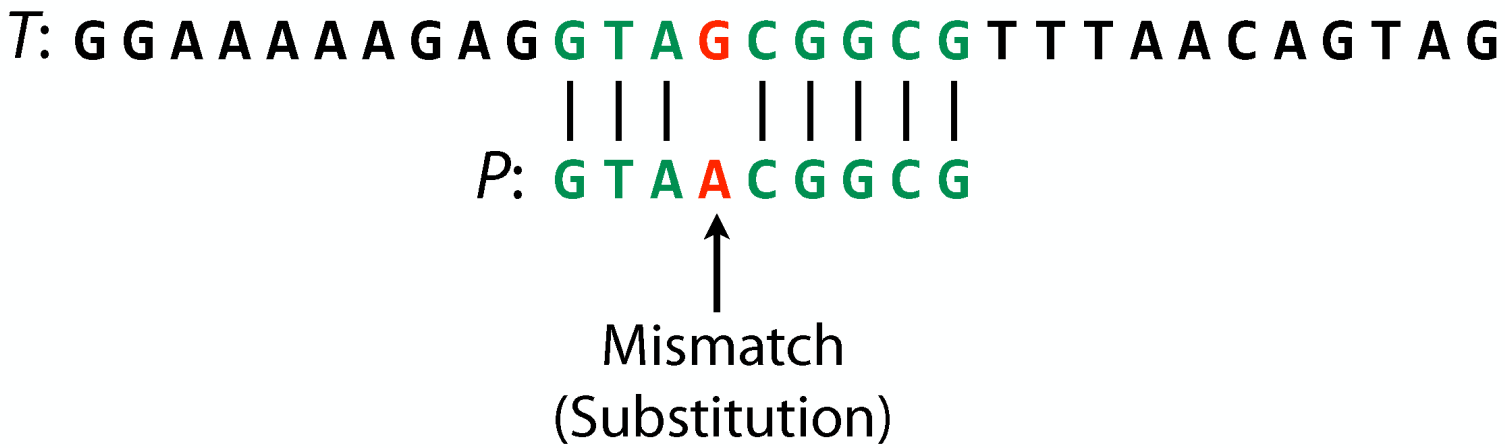
Global Alignment

Target Sequence **Reference**

```
5' ACTACTAGATTACTTACGGATCAGGTACTTTAGAGGCTTGCAACCA 3'
   ||||||||||||     |||||||  |||||||||||||| ||||||||
5' ACTACTAGATT----ACGGATC--GTACTTTAGAGGCTAGCAACCA 3'
```

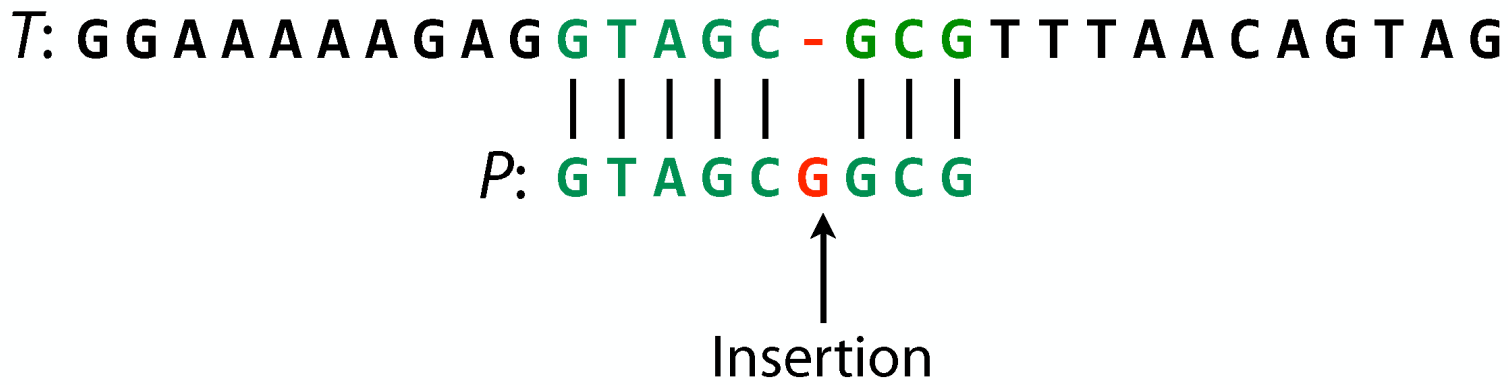
Query Sequence **Reads**

Approximate matching



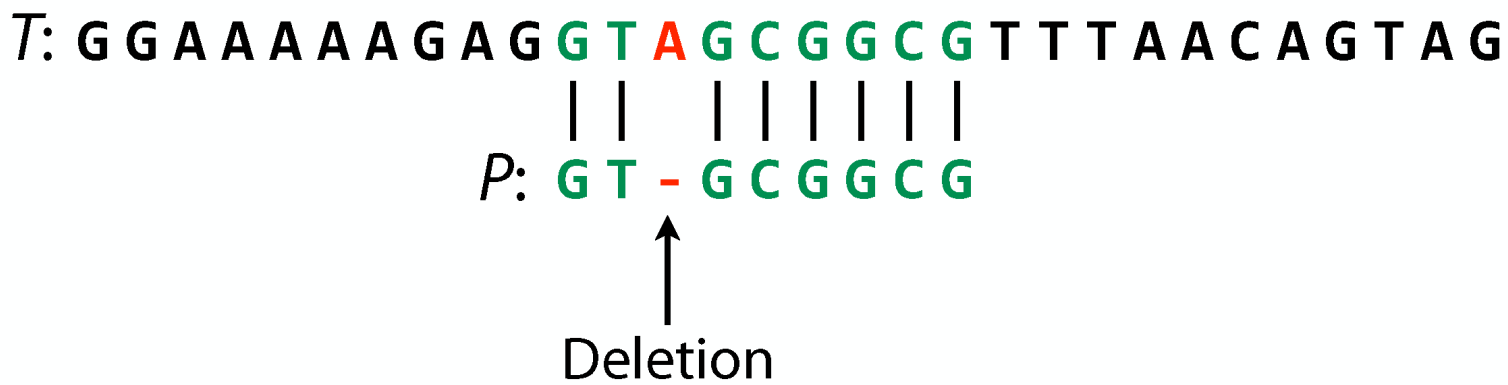
Tolerate more mismatches to accomodate sequencing *errors* and *SNPs*

Approximate matching



allow more gaps

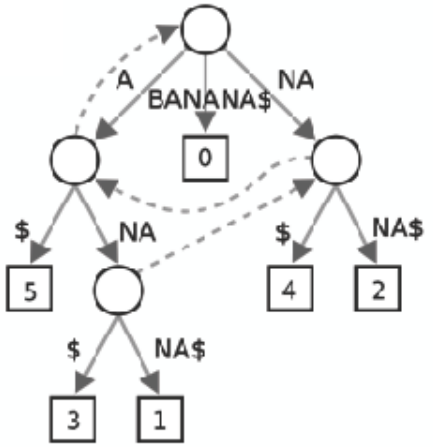
Approximate matching



allow more gaps

Burrows-Wheeler Transform (BWT)

Indexing with suffixes



Suffix Tree

6	$
5	A$
3	ANA$
1	ANANA$
0	BANANA$
4	NA$
2	NANA$

Suffix Array

$	BANANA
A	$BANAN
ANA	$BAN
ANANA	$B
BANANA	$
NA	$BANA
NANA	$BA

FM Index

Suffix arrays are space efficient data structures…

Manber, U., and G. Myers, **1990** Suffix arrays: a new method for on-line string searches, pp. 319–327 in *Proceedings of the first annual ACM-SIAM symposium on Discrete algorithms*. Society for Industrial and Applied Mathematics, San Francisco, California, USA.

Burrows-Wheeler Transform

Reversible permutation of the characters of a string, used originally for compression

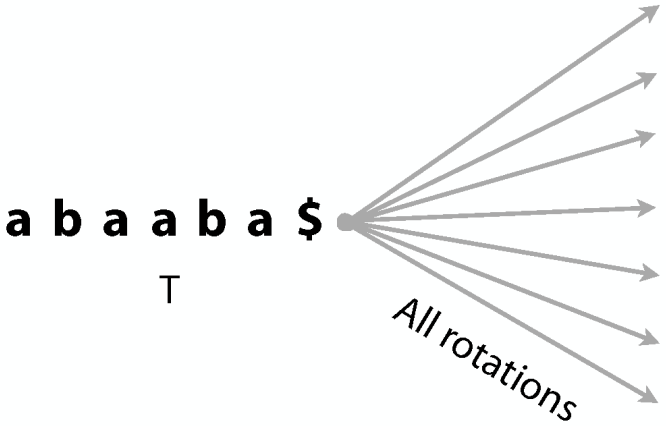
a b a a b a $

T

Burrows M, Wheeler DJ: A block sorting lossless data compression algorithm.
Digital Equipment Corporation, Palo Alto, CA 1994, Technical Report 124; 1994

Burrows-Wheeler Transform

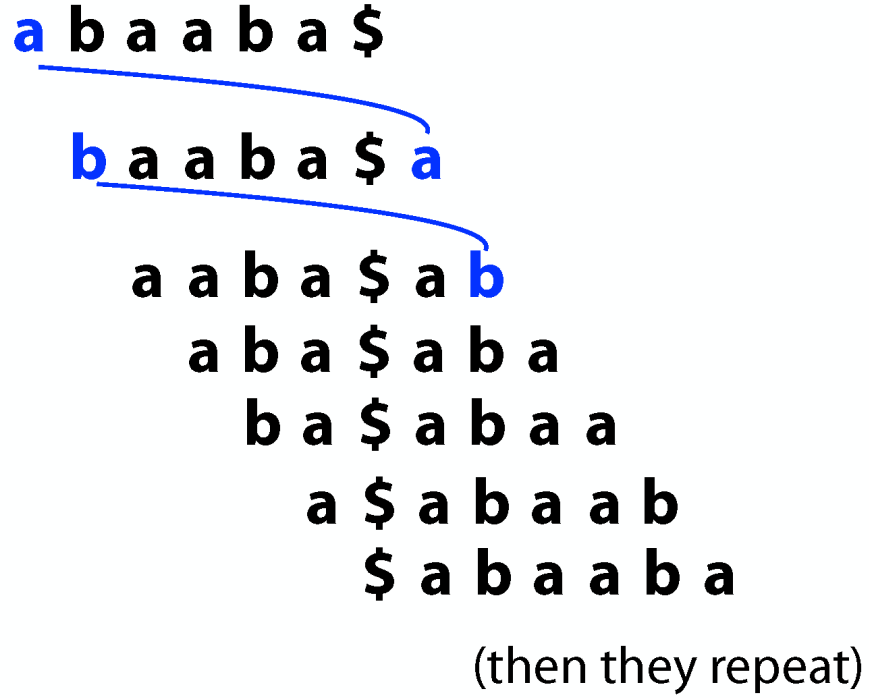
Reversible permutation of the characters of a string, used originally for compression



Burrows M, Wheeler DJ: A block sorting lossless data compression algorithm. *Digital Equipment Corporation, Palo Alto, CA* 1994, Technical Report 124; 1994

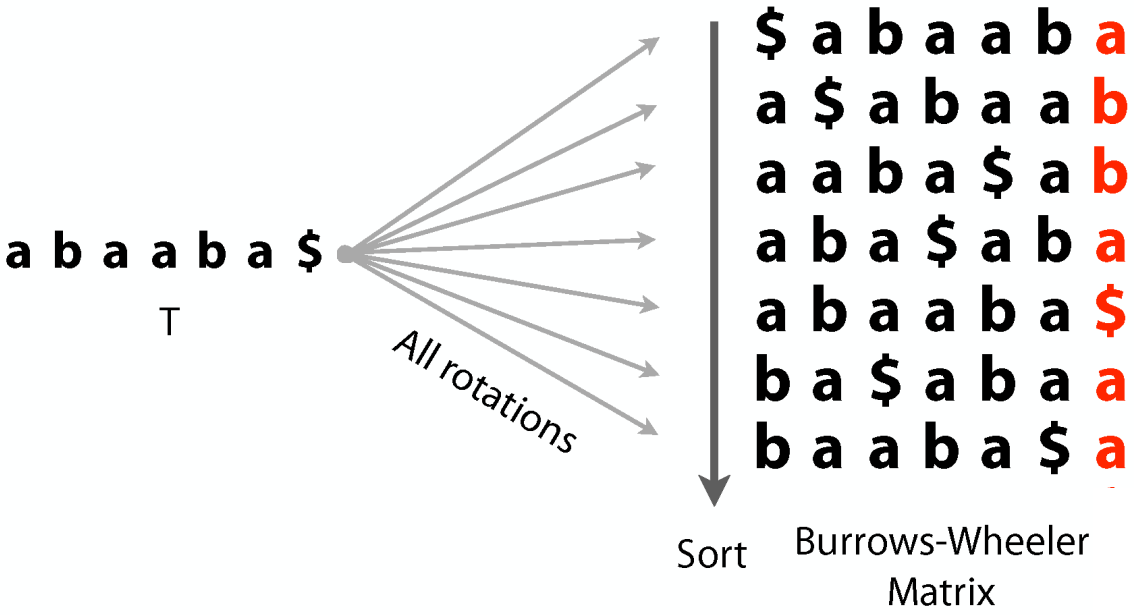
Burrows-Wheeler Transform

All rotations



Burrows-Wheeler Transform

Reversible permutation of the characters of a string, used originally for compression



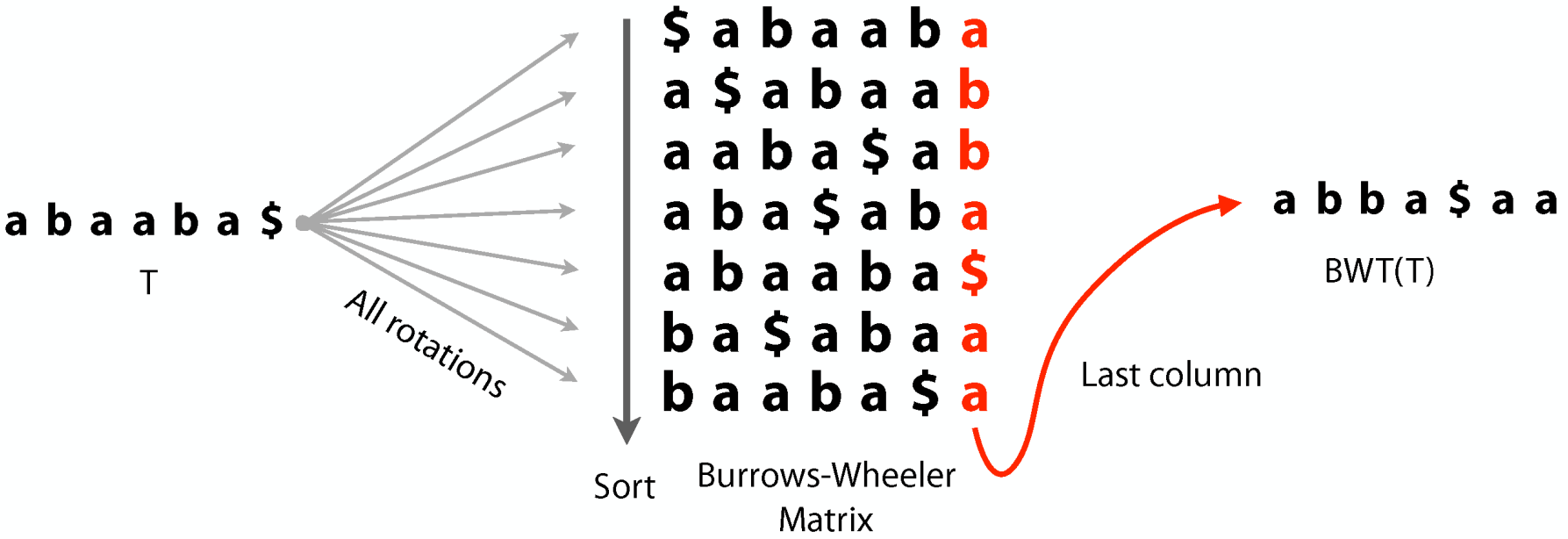
Alphabetical order

BWM

Burrows M, Wheeler DJ: A block sorting lossless data compression algorithm. *Digital Equipment Corporation, Palo Alto, CA* 1994, Technical Report 124; 1994

Burrows-Wheeler Transform

Reversible permutation of the characters of a string, used originally for compression



Burrows M, Wheeler DJ: A block sorting lossless data compression algorithm. *Digital Equipment Corporation, Palo Alto, CA* 1994, Technical Report 124; 1994

BWT in Python Code

```
def rotations(t):
    # Return list of rotations of input string t
    tt = t*2 # this duplicates string t to ensures being able of reading first character after last one
    return [ tt[i:i+len(t)] for i in range(len(t)) ]
```

```
rotations('cat')
```

```
['cat', 'atc', 'tca']
```

```
def bwm(t):
    # Return lexicographically sorted list of t's rotations
    return sorted(rotations(t))
```

```
bwm('abaaba$')
```

```
['$abaaba', 'a$abaab', 'aaba$ab', 'aba$aba', 'abaaba$', 'ba$abaa', 'baaba$a']
```

```
print('\n'.join(bwm('abaaba$')))
```

```
$abaaba
a$abaab
aaba$ab
aba$aba
abaaba$
ba$abaa
baaba$a
```

```
def bwtViaBwm(t):
    # Given T, returns BWT(T) by way of the BWM
    return ''.join(map(lambda x: x[-1], bwm(t)))
```

```
bwtViaBwm('abaaba$') # we can see the result equals the last column of the matrix above
```

```
'abba$aa'
```

BWT features – Repetitive Runs

BWT often shows repetitive patterns

```
# Tendency to show repetitive runs
bwtViaBwm('I_cant_get_no_satisfaction_and_i_try_and_i_try$')
```

```
'y$ynItddtoiif__cs_anngs___ttoaa_anitt_ineca__rr'
```

```
bwtViaBwm('We_all_live_in_a_yellow_submarine_yellow_submarine$')
```

```
'e$neelwwea__mmuunWvnyy_rrll_aeellbbiiillaa__ssioo__'
```

```
bwtViaBwm('You_gotta_run_run_run_run_run_take_a_drag_or_two$')
```

```
'o$eaugannnnnr_trt_ka_auuuuuw_gYod_____t_o_orrrrrt'
```

```
# Repetitive Runs
bwtViaBwm('Tomorrow_and_tomorrow_and_tomorrow$')
```

```
'w$wwdd__nnoooaattTmmmrrrrrrooo__ooo'
```

Allows using Run-Length Encoding

```
bwtViaBwm('You_gotta_run_run_run_run_run_take_a_drag_or_two$')
```

```
'o$eaugannnnnr_trt_ka_auuuuuw_gYod_____t_o_orrrrrt'
```

```
return_encoding_list(bwtViaBwm('You_gotta_run_run_run_run_run_take_a_drag_or_two$'))
```

```
o1$1e1a1u1g1a1n5r1_1t1r1t1_1k1a1_1a1u5w1_1g1Y1o1d1_5t1_1o1_1o1r5t1
```

```
bwtViaBwm('AAAG$GAGAAAGTTTTTGTTGCTA')
```

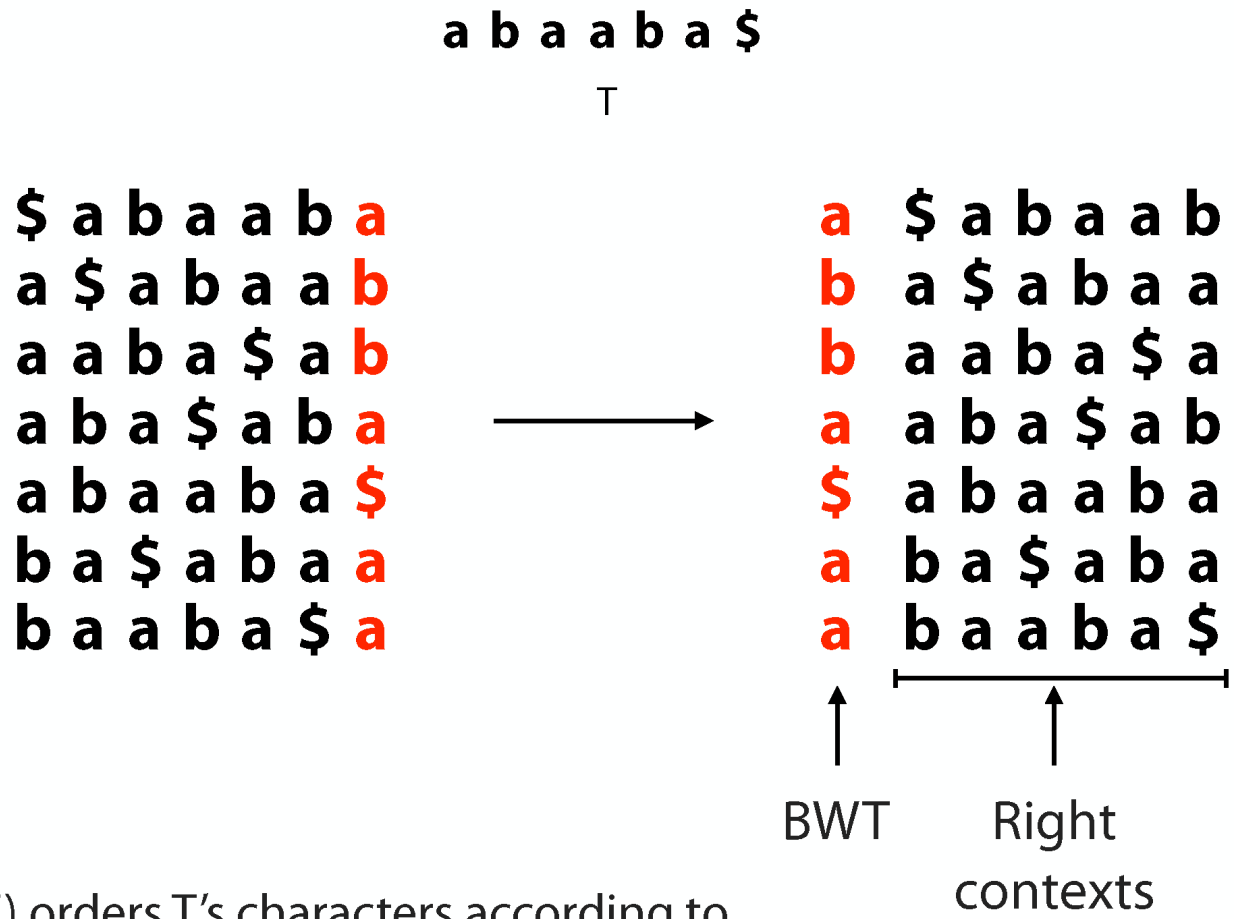
```
'GTAGAAAGAGAA$TTACTTGTTTG'
```

```
return_encoding_list(bwtViaBwm (Read))
```

```
A3G1$1G1A1G1A3G1T5G1T2G1C1T1A1
```

BWT features - The right contexts

Burrows-Wheeler Transform

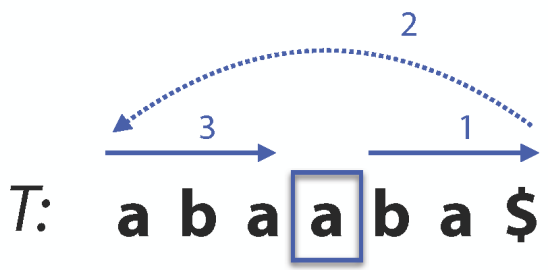


BWT(T) orders T's characters according to alphabetical order of their right contexts in T

Right context

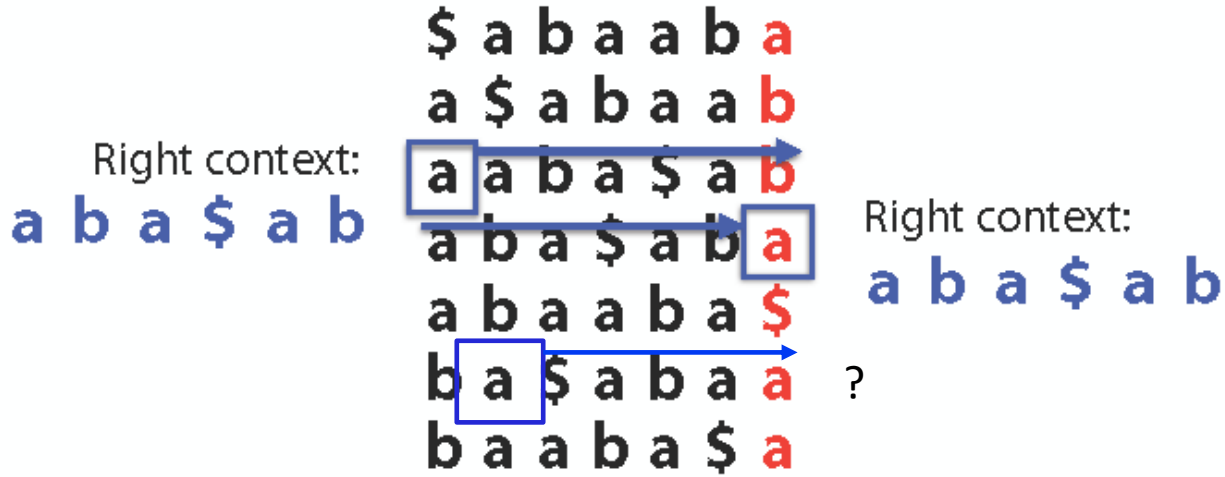
The right context of a position in *T* consists of everything that comes after it with "wrap around"

Right context: **b a a b a $**



Right context: **b a $ a b a**

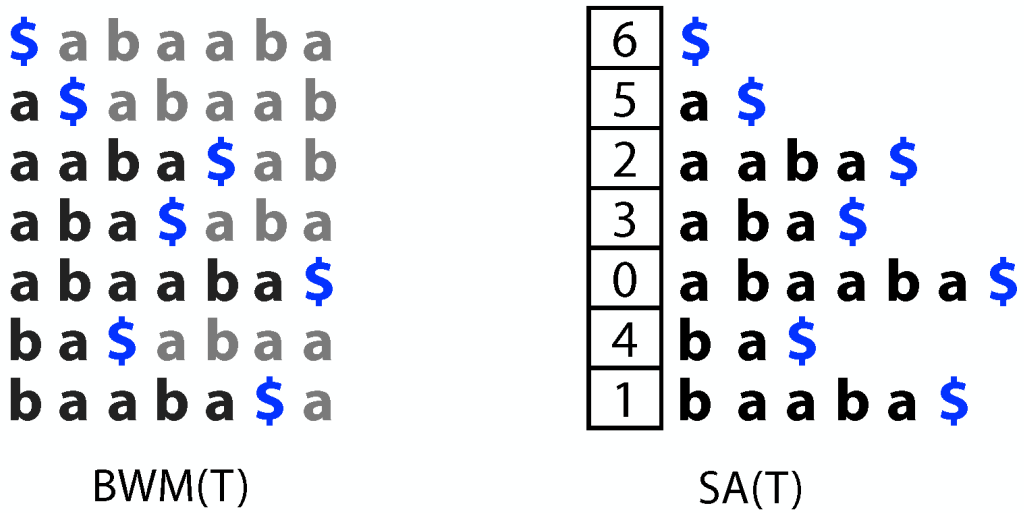
Burrows-Wheeler Transform



BWT can be obtained from the Suffix Array

Burrows-Wheeler Transform

BWM is related to the suffix array



BWM(T) SA(T)

Same order whether rows are rotations or suffixes

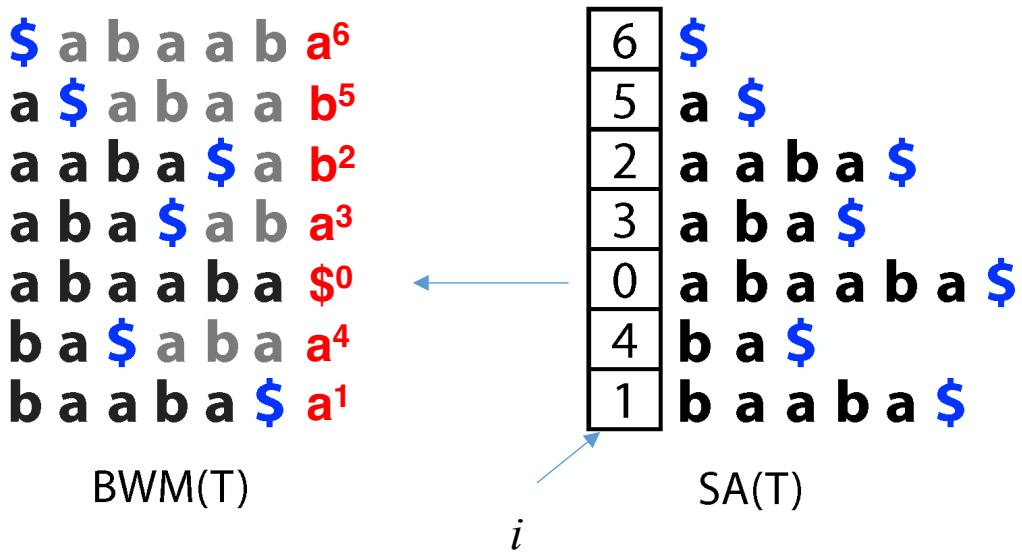
The suffix is the right-context

Burrows-Wheeler Transform

In fact, this gives us a new definition / way to construct BWT(T):

$$BWT[i] = \begin{cases} T[SA[i]-1] & \text{if } SA[i] > 0 \\ \$ & \text{if } SA[i] = 0 \end{cases}$$

"BWT = characters just to the left of the suffixes in the suffix array"



i determines the position of the character *before* the suffix

FM Index

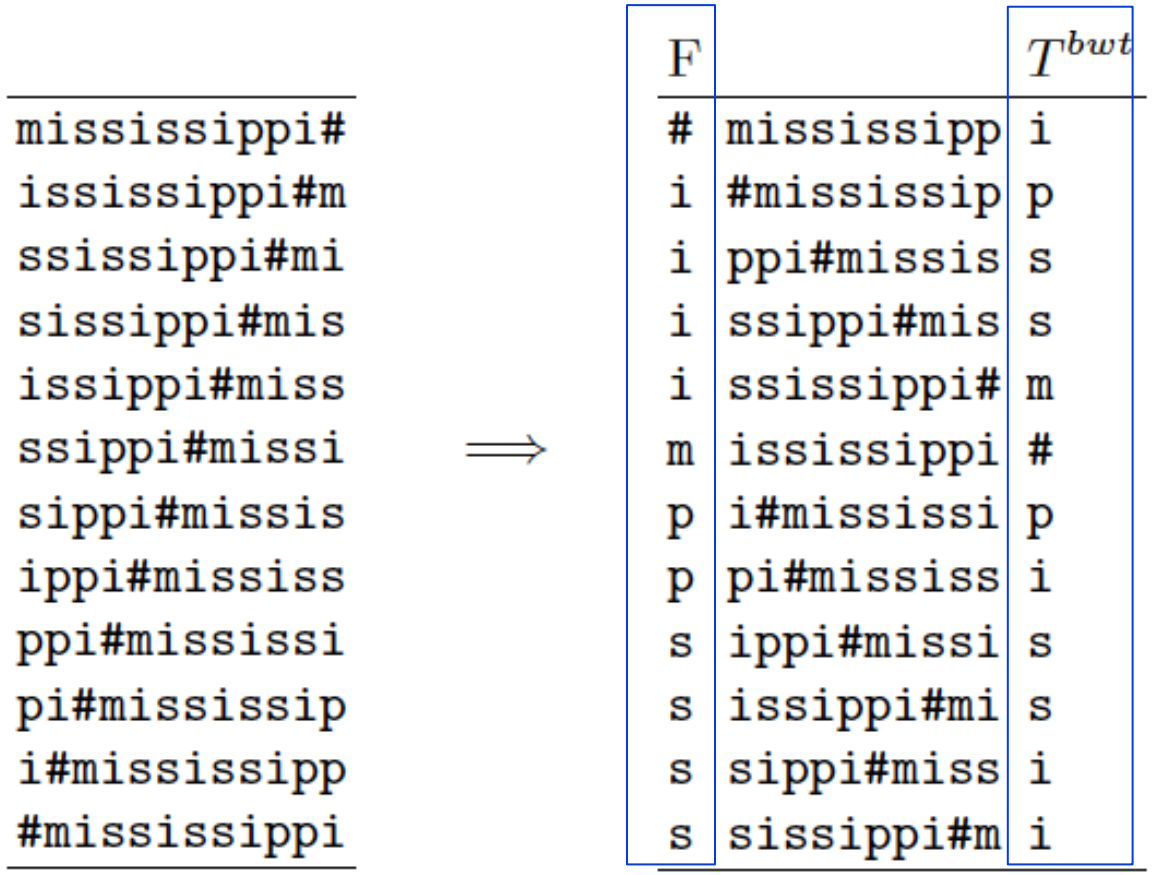


Fig. 1. Example of Burrows-Wheeler transform for the string $T =$ `mississippi`. The matrix on the right has the rows sorted in lexicographic order. The output of the BWT is the last column; in this example the string `ipssm#pissii`.

Ferragina, Manzini et al. **An Alphabet-Friendly FM-Index.** (*SPIRE,* 2004)

Why is enough to store the First and Last Column of Burrows Wheeler Matrix (BWM)?

Burrows-Wheeler Transform: T-ranking

Give each character in *T* a rank, equal to # times the character occurred previously in *T*. Call this the *T-ranking*.

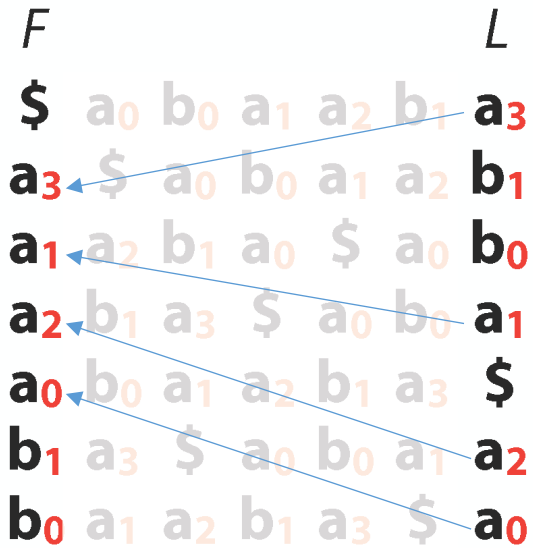
a_0 b_0 a_1 a_2 b_1 a_3 $

Ranks aren't explicitly stored; they are just for illustration

Now let's re-write the BWM including ranks...

Burrows-Wheeler Transform: LF Mapping

BWM with T-ranking:

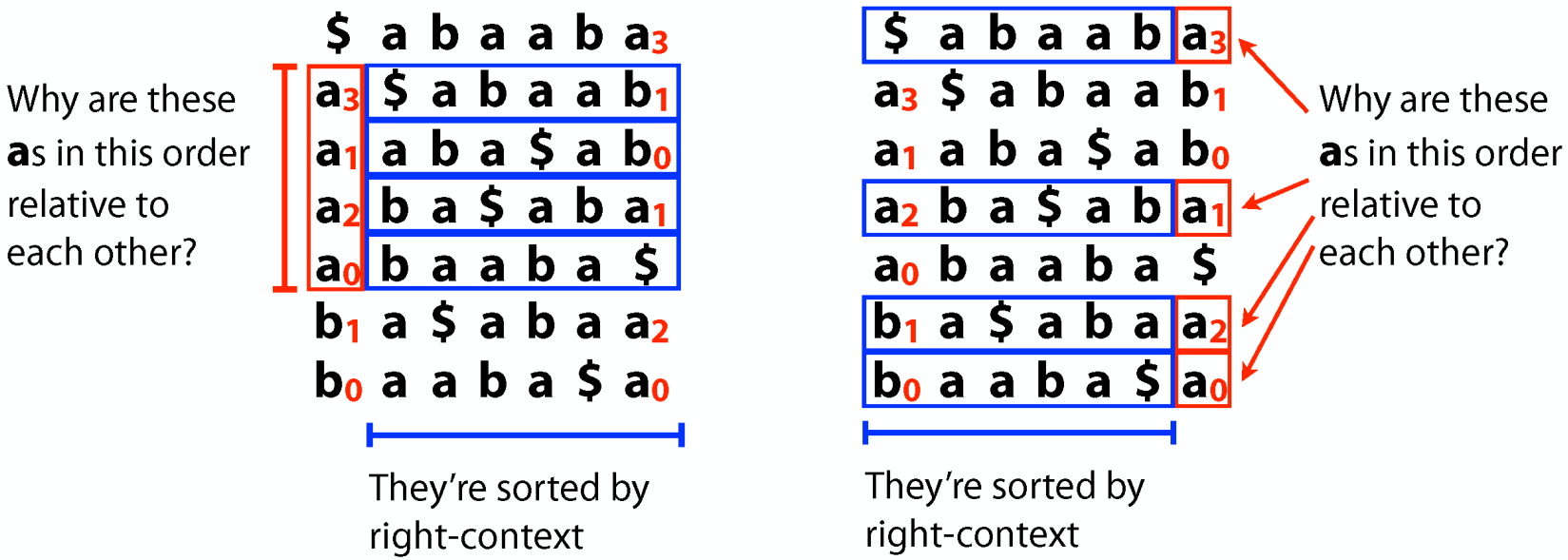


LF Mapping: The i^{th} occurrence of a character c in L and the i^{th} occurrence of c in F correspond to the *same* occurrence in T (i.e. have same rank)

However we rank occurrences of c, ranks appear in the same order in F & L

Burrows-Wheeler Transform: LF Mapping

Why does the LF Mapping hold?



Occurrences of *c* in *F* are sorted by right-context. Same for *L*!

Whatever ranking we give to characters in *T*, rank orders in *F* and *L* will match

FM Index

e.g. ranks

FM Index: an index combining the BWT *with a few small auxiliary data structures*

Core of index is ***F*** and ***L*** from BWM:

L is the same size as *T*

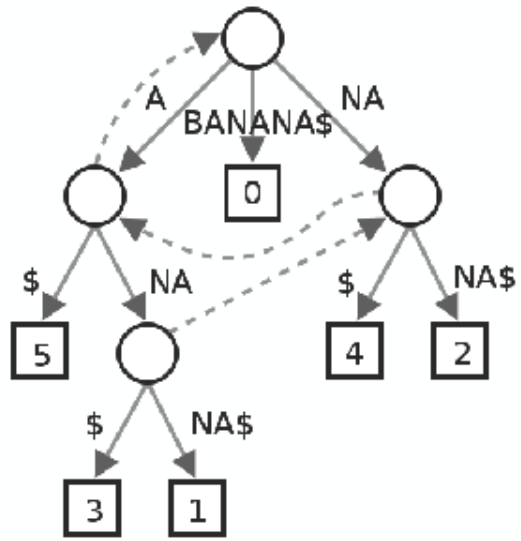
F can be represented as array of |Σ| integers

L is compressible (but even uncompressed, it's small compared to suffix array)

We *can recreate the original string* from right to left (LF-mapping property)

Paolo Ferragina, and Giovanni Manzini. "Opportunistic data structures with applications." *Foundations of Computer Science, 2000. Proceedings. 41st Annual Symposium on*. IEEE, 2000.

FM Index: small memory footprint



Suffix tree

≥ 45 GB

6	$
5	A$
3	ANA$
1	ANANA$
0	BANANA$
4	NA$
2	NANA$

Suffix array

≥ 12 GB

$ B A N A N A
A $ B A N A N
A N A $ B A N
A N A N A $ B
B A N A N A $
N A $ B A N A
N A N A $ B A

FM Index

~ 1.5 GB

https://langmead-lab.org/teaching-materials/

Hands-on Exercises in Python

Let's put in practice what we have been learning Ex. 9.1:

1) Build Matrix BWM
2) Burrows-Wheeler BWT
3) Obtain FM Index from BWT

In addition, Ex. 9.2:

4) Algorithm for Run-Length Encoding of DNA Sequences