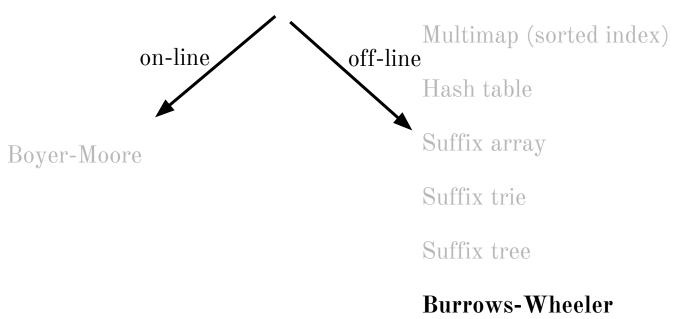
Burrows-Wheeler Transform and FM Index

Lesson 04

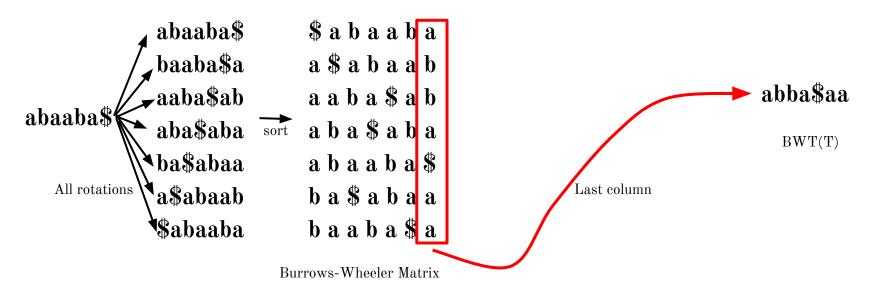
Recapitulation

Exact string matching algorithms



transform + FM index





How is it useful for compression?

How is it reversible?

How is it an index?

```
def rotations(t):
    """ Return list of rotations of input string t """
    tt = t * 2
    return [tt[i:i+len(t)] for i in range(0, len(t))]

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

def bwtViaBwm(t):
    """ Given T, returns BWT(T) by creating BWM """
    return ''.join(map(lambda x: x[-1], bwm(t)))
Take last column
```

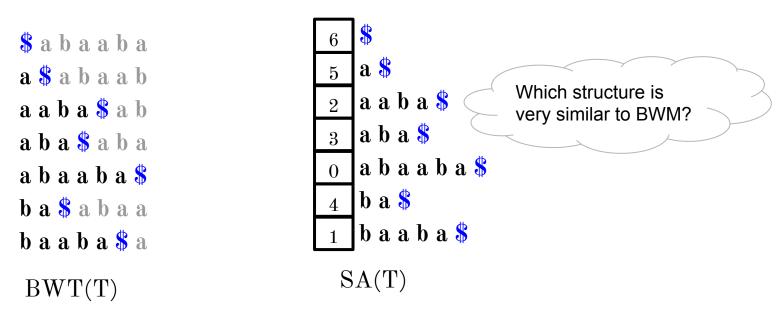
```
>>> bwtViaBwm("Tomorrow_and_tomorrow_and_tomorrow$")
'w$wwdd__nnoooaattTmmmrrrrrooo__ooo'
>>> bwtViaBwm("It_was_the_best_of_times_it_was_the_worst_of_times$")
's$esttssfftteww_hhmmbootttt_ii__woeeaaressIi_____'
>>> bwtViaBwm('in_the_jingle_jangle_morning_Ill_come_following_you$')
'u_gleeeengj_mlhl_nnnnt$nwj__lggIolo_iiiiarfcmylo_oo_'
```

- Characters of the BWT are sorted by their right-context

 Right-context from 'a'
- This lends additional structure to BWT(T), tending to make it more compressible

Burrows-Wheeler Matrix

BWM bears a resemblance to the suffix array



Sort order is the same whether rows are rotations or suffixes

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

BWT(T)

6 \$
5 a \$
2 a a b a \$
3 a b a \$
0 a b a a b a \$
4 b a \$
1 b a a b a \$

SA(T)

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

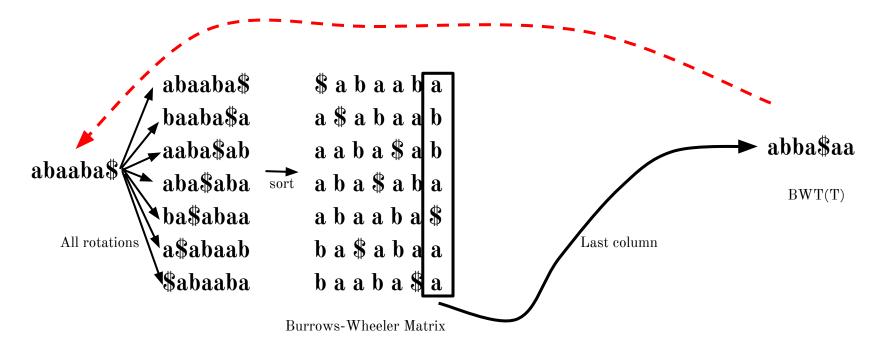
```
def suffixArray(s):
    """ Given T return suffix array SA(T). We use Python's sorted
        function here for simplicity, but we can do better. """
    satups = sorted([(s[i:], i) for i in range(len(s))])
    # Extract and return just the offsets
    return map(lambda x: x[1], satups)

def bwtViaSa(t):
    """ Given T, returns BWT(T) by way of the suffix array. """
    bw = []
    for si in suffixArray(t):
        if si == 0: bw.append('$')
        else: bw.append(t[si-1])
    return ''.join(bw) # return string-ized version of list bw
```

Make suffix array

Take characters just to the left of the sorted suffixes

```
>>> bwtViaBwm("Tomorrow_and_tomorrow_and_tomorrow$")
'w$wwdd__nnoooaattTmmmrrrrrrooo__ooo'
>>> bwtViaBwm("It_was_the_best_of_times_it_was_the_worst_of_times$")
's$esttssfftteww_hhmmbootttt_ii__woeeaaressIi_____'
>>> bwtViaBwm('in_the_jingle_jangle_morning_Ill_come_following_you$')
'u_gleeeengj_mlhl_nnnnt$nwj__lggIolo_iiiiarfcmylo_oo_'
```



How to reverse the BWT?

BWM has a key property called the LF Mapping

Burrows-Wheeler Transform: T-ranking

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

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

Burrows-Wheeler Transform: T-ranking

BWT with T-raking: \$ a_0 b_0 a_1 a_2 b_1 a_3 \$ a_0 b_0 a_1 a_2 b_1 a_2 b_1 a_3 \$ a_0 b_0 a_1 a_2 b_1 a_3 \$ a_0 b_0 a_1 a_2 b_1 a_2 b_1 a_3 \$ a_0 b_0 a_1 a_2 b_1 a_2 b_1 a_2 b_1 a_3 \$ a_0 b_0 a_1 a_2 b_1 a_2 b_1 a_3 \$ a_0 b_0 a_1 a_2 b_1 a_2 b_1 a_2 b_1 a_3 \$ a_0 b_0 a_1 a_2 b_1 a_2 b_2

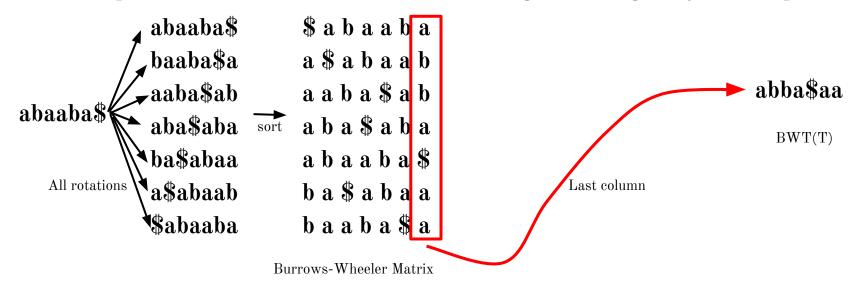
Look at first and last columns, called F and L
"a" occur in the same order in F and L
As we look down columns, in both cases we see: a₃, a₁, a₂, a₀

Burrows-Wheeler Transform: T-ranking

BWT with T-raking: \$

Same is with "b"

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



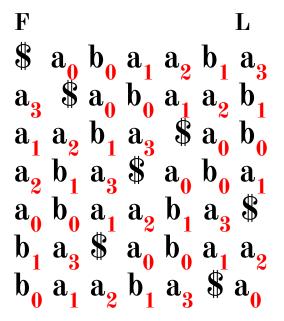
How is it useful for compression?

How is it reversible?

How is it an index?

Burrows-Wheeler Transform: LF Mapping

BWT with T-raking:



Order of ranks in L is preserved in F!

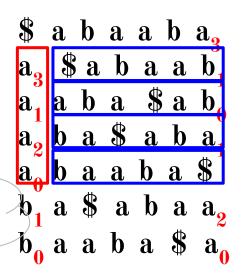
LF Mapping: The i-th occurrence of a character c in L and the i th occurrence of c in F correspond to the same occurrence in T

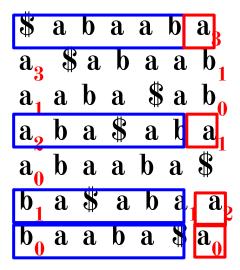
However we rank occurrences of c, ranks appear in the same order in F and L

Burrows-Wheeler Transform: LF Mapping

Why does the LF Mapping hold? Why are these "a" in this order relative to each other?

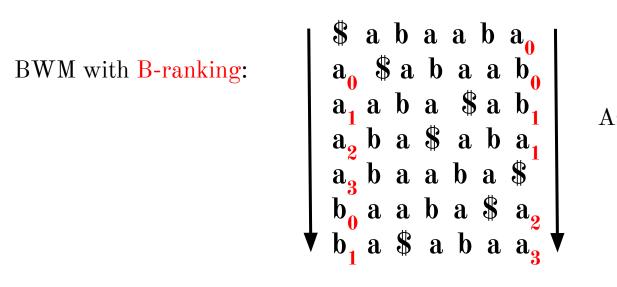
They're sorted by right-context!!!





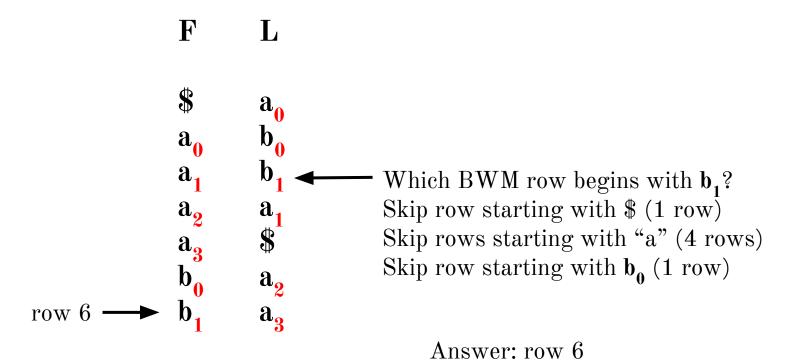
Occurrences of c in F are sorted by right-context. Same for L! Whatever ranking we give to characters in T, rank orders in F and L will match

Burrows-Wheeler Transform: LF Mapping



Ascending rank

F now has very simple structure: a \$, a block of "a" with ascending ranks, a block of "b" with ascending ranks (we do not have to store its ranks)



Say T has 300 As, 400 Cs, 250 Gs and 700 Ts and \$ < A < C < G < T Which BWM row (0-based) begins with G_{100} ? (Ranks are B-ranks.)

- Skip row starting with \$ (1 row)
- Skip rows starting with A (300 rows)
- Skip rows starting with C (400 rows)
- Skip first 100 rows starting with G (100 rows)
- Answer: row 1 + 300 + 400 + 100 = row 801

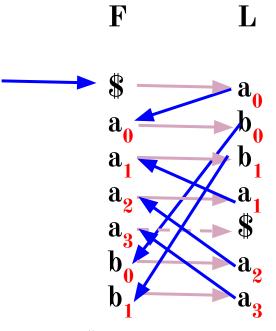
Burrows-Wheeler Transform: reversing

Reverse BWT(T) starting at right-hand-side of T and moving left

Start in first row. F must have \$.

L contains character just prior to \$: \mathbf{a}_0

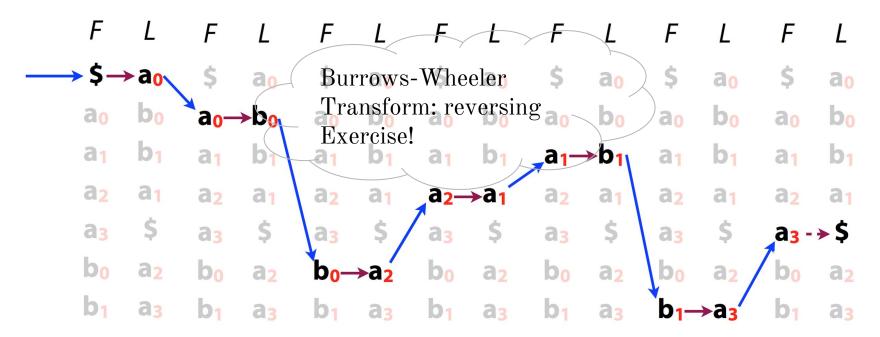
• • •



Reverse of chars we visited $= a_3 b_1 a_1 a_2 b_0 a_0$ \$ = T

Burrows-Wheeler Transform: reversing

Another way of visualizing Reverse BWT(T)



Burrows-Wheeler Transform: reversing

We've seen how BWT is useful for compression:

Sorts characters by right-context, making a more compressible string

And how it's reversible:

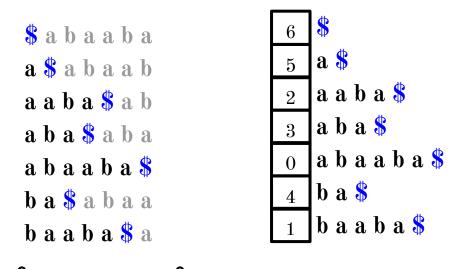
Repeated applications of LF Mapping, recreating T from right to left

How is it used as an index?

FM index

- An index combining the BWT with a few small auxiliary data structures "FM" supposedly stands for "Full-text Minute-space." (But inventors are named Ferragina and Manzini)
 - Core of index consists of F and L from BWM:
 - F can be represented very simply (1 integer per alphabet character)
 - And L is compressible
 - Potentially very space-economical!

Though BWM is related to suffix array, we can't query it the same way



We don't have these columns; binary search isn't possible

Look for range of rows of BWM(T) with P as prefix Do this for P's shortest suffix, then extend to successively longer suffixes until range becomes empty or we've exhausted P

Easy to find all the rows beginning with a, thanks to F's simple structure \$ a b a a b a₀

a₀ \$ a b a a b a₀

a₁ a b a \$ a b₁

a₂ b a \$ a b a \$

b₀ a a b a \$ a₂

b₁ a \$ a b a a₃

P = aba

Look for range of rows of BWM(T) with P as prefix Do this for P's shortest suffix, then extend to successively longer suffixes until range becomes empty or we've exhausted P

$$P = aba$$

Look at those rows in L.

 b_0 , b_1 are b-s occurring just to left.

Use LF Mapping. Let new range delimit those b-s b₁ a a b a b a a₂

$$P = aba$$

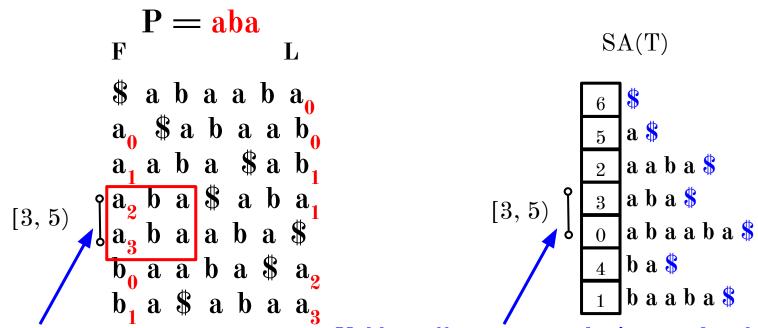
\$ a b a a b a₀
a₀ \$ a b a a b₀
a₁ a b a \$ a b₁
a₂ b a \$ a b a
a₃ b a a b a \$
b₀
a a b a \$ a₂
b
a \$ a b a \$
a₃

We have rows beginning with ba, now we seek rows beginning with aba

Now we have the rows with prefix aba

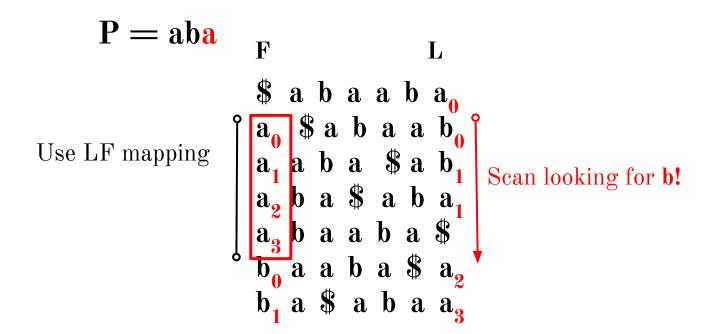
When P does not occur in T, we will eventually fail to find the next character in L:

We have rows beginning with ba, now we seek rows beginning with aba



Where are these?

Unlike suffix array, we don't immediately know where the matches are in T...



FM Index: Current issues

(1) Scanning for preceding character is slow

```
$ a b a a b a<sub>0</sub>

a<sub>0</sub> $ a b a a b<sub>0</sub>
a<sub>1</sub> a b a $ a b<sub>1</sub>
a<sub>2</sub> b a $ a b a $
b<sub>0</sub> a a b a $ a<sub>2</sub>
b<sub>1</sub> a $ a b a a<sub>2</sub>
```

```
(2) Storing ranks takes too much space
```

```
def reverseBwt(bw):
    ''' Make T from BWT(T) '''
    ranks, tots = rankBwt(bw)
    first = firstCol(tots)
    rowi = 0 # start in first row
    t = '$' # start with rightmost character
    while bw[rowi] != '$':
        c = bw[rowi]
        t = c + t # prepend to answer
        # jump to row that starts with c of same rank
        rowi = first[c][0] + ranks[rowi]
    return t
```

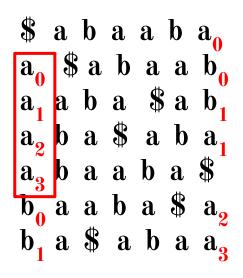
(3) Need way to find where a_0 \$ a b a a b_0 matches occur in T: a_1 a b a \$ a b_1

[3, 5)
Where are these?

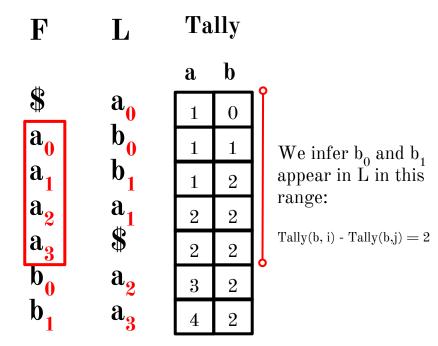
\$ a b a a b a₀
re a₀ \$ a b a a b₀
a₁ a b a \$ a b₁
a₂ b a \$ a b a₁
a₃ b a a b a \$
b₀ a a b a \$ a₂
b a \$ a b a \$

FM Index: fast rank calculations

Is there an O(1) way to determine which **b** precede the **a** in our range?



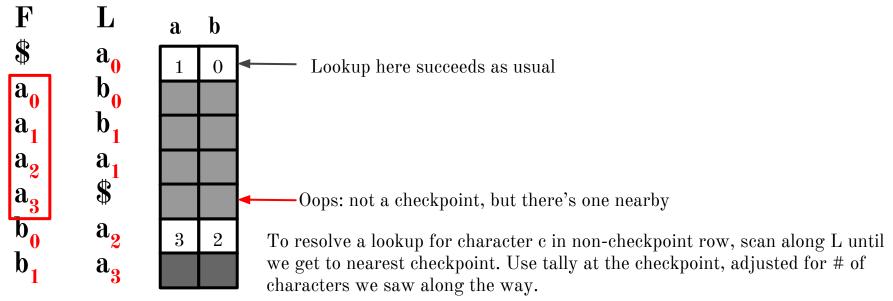
Idea: pre-calculate # a-s, b-s in L up to every row:



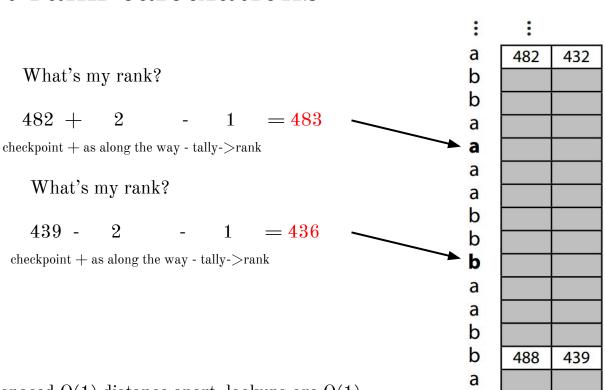
O(1) time, but requires m $\times |\Sigma|$ integers

FM Index: fast rank calculations

Another idea: pre-calculate # as, bs in L up to some rows, e.g. every 5th row. Call pre-calculated rows checkpoints.



FM Index: fast rank calculations



What's my rank?

439 - 2 - 1 = 436

Assuming checkpoints are spaced O(1) distance apart, lookups are O(1)

Tally

b

FM Index: Current issues

(1) Scanning for preceding character is slow

```
$ a b a a b a<sub>0</sub>

a<sub>0</sub> $ a b a a b<sub>0</sub>
a<sub>1</sub> a b a $ a b<sub>1</sub>
a<sub>2</sub> b a $ a b a<sub>1</sub>
a<sub>3</sub> b a a b a $
b<sub>0</sub> a a b a $ a<sub>2</sub>
b<sub>1</sub> a $ a b a a<sub>3</sub>
```

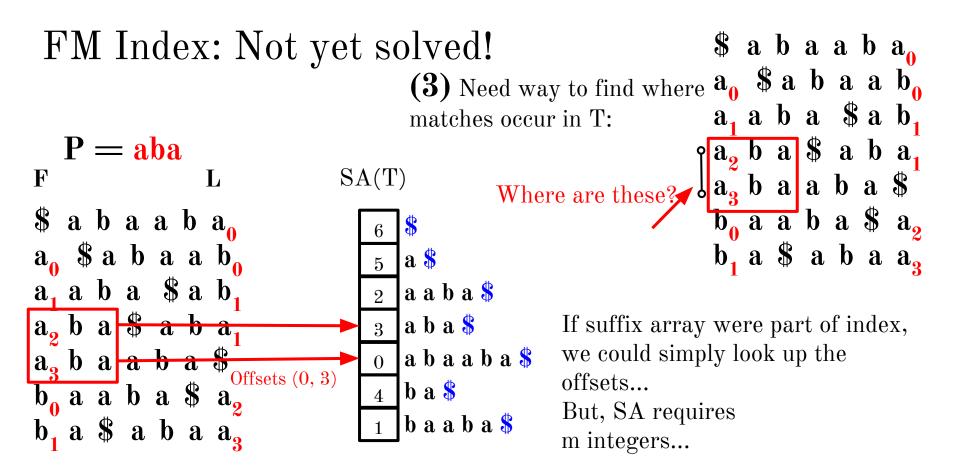
With checkpoints it's O(1)

```
(2) Storing ranks takes too much space
```

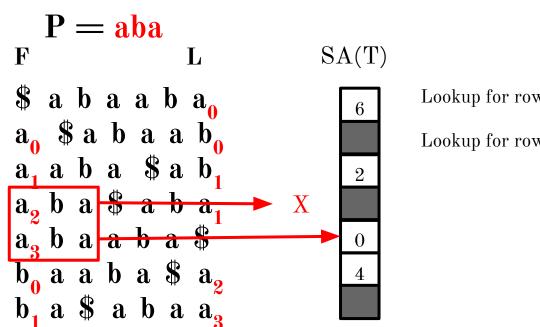
```
def reverseBwt(bw):
    ''' Make T from BWT(T) '''
    ranks, tots = rankBwt(bw)
    first = firstCol(tots)
    rowi = 0 # start in first row
    t = '$' # start with rightmost character
    while bw[rowi] != '$':
        c = bw[rowi]
        t = c + t # prepend to answer
        # jump to row that starts with c of same rank
        rowi = first[c][0] + ranks[rowi]
    return t
```

With checkpoints, we greatly reduce # integers needed for ranks - but it's still O(m) space - there's literature

on how to improve this space bound



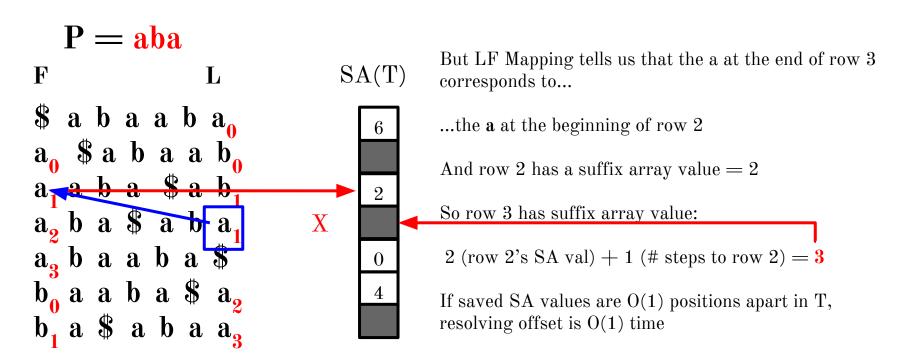
FM Index: resolving offsets



Lookup for row 4 succeeds - we kept that entry of SA

Lookup for row 3 fails - we discarded that entry of SA

FM Index: resolving offsets

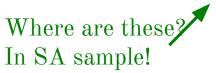


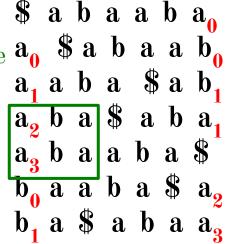
FM Index: resolving offsets

SA sample(T)



(3) Need way to find where $\mathbf{a_0}$ \$ a b a a $\mathbf{b_0}$ matches occur in T $\mathbf{a_1}$ a b a \$ a b.





With SA sample we can do this in O(1) time per occurrence

FM Index: small memory footprint

Components of the FM Index:

First column (F): $\sim |\Sigma|$ integers

Last column (L): m characters

SA sample: $m \cdot a$ integers, where a is fraction of rows kept

Checkpoints: $m \times |\Sigma| \cdot b$ integers, where b is fraction of

rows checkpointed

Example: DNA alphabet (2 bits per nucleotide), T = human genome,

a = 1/32, b = 1/128

First column (F): 16 bytes

Last column (*L*): 2 bits * 3 billion chars = 750 MB

SA sample: 3 billion chars * 4 bytes/char / $32 = \sim 400 \text{ MB}$

Checkpoints: 3 billion * 4 bytes/char / 128 = ~ 100 MB

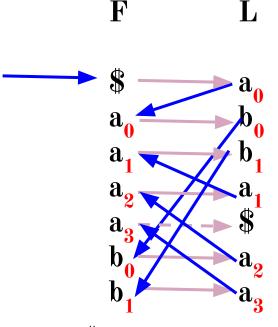
Total < 1.5 GB

One more time: BWT reversing

Reverse BWT(T) starting at right-hand-side of T and moving left

Start in first row. F must have \$. L contains character just prior to \$: a₀

. . .



Reverse of chars we visited $= a_3^{} b_1^{} a_1^{} a_2^{} b_0^{} a_0^{} \$ = T$

One more time: BWT FM Index - querying

Look for range of rows of BWM(T) with P as prefix Do this for P's shortest suffix, then extend to successively longer suffixes until range becomes empty or we've exhausted P

$$P = aba$$

Look at those rows in L. b_0 , b_1 are b-s occurring

just to left.

Use LF Mapping. Let new range delimit those b-s b₁ a a b a b a a₂

P = aba

\$ a b a a b a₀
a₀ \$ a b a a b₀
a₁ a b a \$ a b₁
a₂ b a \$ a b a
a₃ b a a b a \$
b₀
a a b a \$ a₂
b
a \$ a b a \$
a₃

One more time: BWT FM Index - querying

We have rows beginning with ba, now we seek rows beginning with aba

Now we have the rows with prefix aba

FM Index

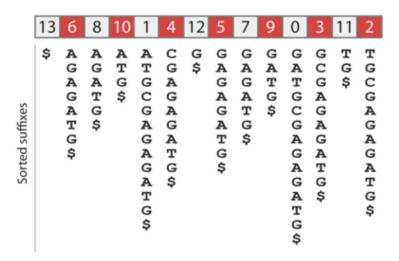
- 1. L = BWT(T)
- 2. First column (number of appearances of each character)
- 3. Suffix Array (or SA Sample)
- 4. Tally (rank, occurrences) matrix

FM Index: Example

Search for:

GAGA

BWT Occ C[A]+Occ(A,1-1) C[A]+Occ(A,13)-1 A C[G]+Occ(G,4)-1 G C[G]+Occ(G,1-1) C[A]+Occ(A,7-1) A C[A]+Occ(A,10)-1 C[G]+Occ(G,2)-1 G C[G]+Occ(G,1-1)





FASTQ

```
@SEQ_ID
GATTTGGGGTTCAAAGCAGTATCGATCAAATAGTAAATCCATTTGTTCAACTCACAGTTT
+
!''*((((***+))%%%++)(%%%%).1***-+*''))**55CCF>>>>>CCCCCCC65
```

A FASTQ (FQ) file normally uses four lines per sequence.

- Line 1 begins with a '@' character and is followed by a sequence identifier and an optional description.
- Line 2 is the raw sequence letters.
- Line 3 begins with a '+' character and is optionally followed by the same sequence identifier (and any description) again.
- Line 4 encodes the quality values for the sequence in Line 2, and must contain the same number of symbols as letters in the sequence.

FASTA

> CONTIG NAME

GATTTGGGGTTCAAAGCAGTATCGATCAAATAGTAAATCCATTTGTTCAACTCACAGTTT
GATTTGGGGTTCAAAGCAGTAATTTGGGGTTCAAAGCAGTATCGACAAATAGTAAATCCA
TTTGTTCATTCAAAGCAGTAATTTGGGGTTATTTGGGGTTCAAAGCAGTATCGATCAAAT
AGTAAATCCATTTGTTCAACTCACAGTTT
GATT

FASTA is used for storing the sequence of nucleotides or amino acids

What is CIGAR string?

• Describes similarity between sequences

```
RefPos: 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 Reference: C C A T A C T G A A C T G G C T Read:
```

POS: 5

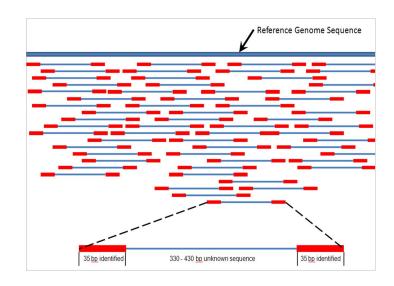
CIGAR: 3M1I3M1D5M

```
D - delete, I - insert, M - match/mismatch, H - hard clip, S - soft clip, N - skipped from the sequence, P - padding silent
```

BWA-MEM

bwa mem ref.fa read1.fq read2.fq > aln.sam

- http://bio-bwa.sourceforge.net/
- Reference genome index must exist
- Paired-end reads
- Primary and secondary alignment (random)



BWA-MEM output

Line from SAM file:

QNAME	SRR035022.2621862		
FLAG	163		
RNAME	16		
POS	59999		
MAQ	37		
CIGAR	22S54M		
MRNM	=		
MPOS	60102		
ISIZE	179		
SEQ	CCAACCCAACCCTAACCCTAACCCTAACCCTAACCCTAACCCTAACCCTAACCCTAACCGACCCTCACCCTCACCC		
QUAL	>AAA=>?AA>@@B@B?AABAB?AABAB?AAC@B?@AB@A?A>A@A?AAAAB??ABAB?79A?AAB;B?@?@<=8:8		
TAG	XT:A:M		
TAG	XN:i:2		
TAG	SM:i:37		
TAG	AM:i:37		
TAG	XM:i:0		
TAG	XO:i:0		
TAG	XG:i:0		
TAG	RG:Z:SRR035022		
TAG	NM:i:2		
TAG	MD:Z:0N0N52		
TAG	OQ:Z:CCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCC		

1 the read is paired in sequencing, no matter whether it is mapped in a pair
1 the read is mapped in a proper pair
0 not unmapped
0 mate is not unmapped
0 forward strand
1 mate strand is negative
0 the read is not the first read in a pair
1 the read is the second read in a pair

BWA-MEM aligned reads

```
5678901234567890123456789012345
               coor
                       12345678901234
               ref
                       AGCATGTTAGATAA**GATAGCTGTGCTAGTAGGCAGTCAGCGCCAT
Paired-end-
               r001+
                             TTAGATAAAGGATA*CTG
               r002+
                            aaaAGATAA*GGATA
               r003+
                          gcctaAGCTAA
               r004+
                                         ATAGCT
                                                              TCAGC
 Multipart
               r003-
                                                 ttagct TAGGC
               r001-
                                                                CAGCGCCAT
```

Ins & padding Soft clipping

Splicing Hard clipping

```
@SQ SN:ref LN:45
r001 163 ref
                                     39 TTAGATAAAGGATACTA
                30.8M2T4M1D3M =
                                 37
r002
       0 ref
              9 30 356M1P1I4M
                                      Ø AAAAGATAAGGATA
                                  0
                                                     NM:1:1
r003
       0 ref
              9 30 5H6M
                                      0 AGCTAA
r004
       0 ref 16 30 6M14N5M
                                      0 ATAGCTTCAGC
r003
      16 ref 29 30 6H5M
                                      0 TAGGC
                                                     NM:i:0
      83 ref 37 30 9M
r001
                                    -39 CAGCGCCAT
```

BWA-MEM performance on real data

Total reads size [Gb]	Instance	Execution time
13.6	C3.2xlarge (8CPUs, 15GB)	2h,11min
23.8	C3.2xlarge (8CPUs, 15GB)	2h, 45min
100	C3.8xlarge (32CPUs, 60GB)	5h, 30min

References

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



