

Mansoura University Faculty of Computers and Information Department of Computer Science Second Semester: 2020-2021



[MED-145] Genomics: Genome Indexing IIII Burrows Wheeler Transform & FM-index

Grade: Third Year (Medical Informatics Program)

Sara El-Metwally, Ph.D.

Faculty of Computers and Information,

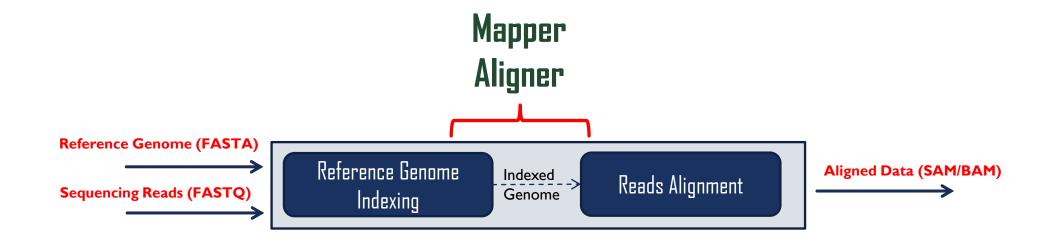
Mansoura University,

Egypt.

AGENDA

- Rev. of Suffix Array & BWT
- Relation of Suffix Array to BWT
- How to use BWT to find the pattern in Genome
- What is FM-index
- How to use FM-index to resolve the query problem over BWT.

TYPICAL MAPPING/ALIGNMENT WORKFLOW



Genome Indexing and Mapping Approaches



REV. (SUFFIX ARRAY) Example:

Construct Suffix Array of GATGCGAGAGATG?

13	6	8	10	1	4	12	5	7	9	0	3	11	2
\$	A	A	A	A	С	G	G	G	G	G	G	T	T
	G	G	T	T	G	\$	A	A	A	A	C	G	G
	A	A	G	G	A		G	G	T	T	G	\$	C
	G	T	\$	C	G		A	A	G	G	A		G
	A	G		G	A		G	T	\$	C	G		A
	T	\$		A	G		A	G		G	A		G
	G			G	A		T	\$		A	G		A
	\$			A	T		G			G	A		G
				G	G		\$			A	T		A
				A	\$					G	G		T
				T						A	\$		G
				G						T			\$
				\$						G			
										\$			

REV. (BWT)

Example:

Construct BWT of GATGCGAGAGATG?

BWT(GATGCGAGAGATG\$) = GGGGGGTCAA\$TAA

NOTES Genome (FASTA): GATGCGAGAGATG



Genome



13	6	8	10	1	4	12	5	7	9	0	3	11	2
----	---	---	----	---	---	----	---	---	---	---	---	----	---

Suffix Array



BWT

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

i	SA[i]	SA[i] -1	T[SA[i]-1]
0	13	12	T[12]=G

NOTES Genome (FASTA): GATGCGAGAGATG



Genome



Suffix Array

C	C	C	C	C	C	The same	Δ	Δ	S	The same	7	Z
9	G	G	G	G	9	-			Y	_		
		/										

BWT

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

i	SA[i]	SA[i] -1	T[SA[i]-1]
1	6	5	T[5]=G

NOTES Genome (FASTA): GATGCGAGAGATG



Genome



Suffix Array

G	G	G	G	G	G	T	C	A	A	\$ T	A	A

BWT

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

i	SA[i]	SA[i] -1	T[SA[i]-1]
10	0		\$

Burrows Wheeler Matrix.

- 1		
~ .	ATGCGAGAGA	
2	AIGCGAGAGA:	G

ACAGATG\$GATGCG

ACATG\$GATGCGI.G

A'TG\$GATGCGAGI.G

A'TGCGAGAGATG: G

CGAGAGATG\$GATG

G GATGCGAGAGAT

GAGAGATG\$GAT(C

GAGATG\$GATGCGA

GATG\$GATGCGAGA

GATGCGAGAGAT(\$

GCGAGAGATG\$GAT

TG\$GATGCGAGAGA

recgagagatg\$(<mark>a</mark>

0	1	2	3	4	5	6	7	8	9	10	11	12	13
G	A	T	G	С	G	A	G	A	G	A	T	G	\$

Sorted Suffixes

13	6	8	10	1	4	12	5	7	9	0	3	11	2
\$	A	A	A	A	С	G	G	G	G	G	G	T	T
	G	G	T	T	G	\$	A	A	A	A	С	G	G
	A	A	G	G	A		G	G	T	T	G	\$	C
	G	T	\$	C	G		A	A	G	G	A		G
	A	G		G	A		G	T	\$	C	G		A
	T	\$		A	G		A	G		G	A		G
	G			G	A		T	\$		A	G		A
	\$			A	T		G			G	A		G
				G	G		\$			A	T		A
				A	\$					G	G		T
				T						A	\$		G
				G						T			\$
				\$						G			
										\$			

Burrows Wheeler Matrix.



Burrows Wheeler Matrix.

\$GATGCGAGAGATGo

A₀ GAGATG\$GATGCG₁

A₁GATG\$GATGCGAG₂

A2 TG\$GATGCGAGAG3

A₃ rgcgagagatg\$G4

CoGAGAGATG\$GATG5

G₀\$GATGCGAGAGAT₀

G1AGAGATG\$GATGC0

G2AGATG\$GATGCGA0

G3ATG\$GATGCGAGA1

G4ATGCGAGAGATG\$

G5CGAGAGATG\$GAT1

T₀G\$GATGCGAGAGA2

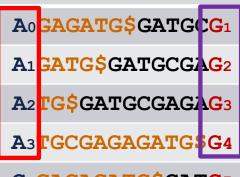
T₁GCGAGAGATG\$GA3

How can we use BWT of the human genome to solve the query problem?



Burrows Wheeler Matrix.

\$GATGCGAGAGATG0



CoGAGAGATG\$GATG5

Go\$GATGCGAGAGATo

G1AGAGATG\$GATGC0

G2AGATG\$GATGCGA0

G3ATG\$GATGCGAGA1

G4ATGCGAGAGATG\$

G5CGAGAGATG\$GAT1

T₀G\$GATGCGAGAGA2

T₁GCGAGAGATG\$GA3

How can we use BWT of the human genome to solve the query problem?



Burrows Wheeler Matrix.

\$GATGCGAGAGATGo

A₀ GAGATG\$GATGCG₁
A₁ GATG\$GATGCGAG₂

A2 TG\$GATGCGAGAG3

A3 **FGCGAGAGATG SG** 4

CoGAGAGATG\$GATG5

Go \$ GATGCGAGAGATo

G1AGAGATG\$GATGC0

G2AGATG\$GATGCGA0

G3ATG\$GATGCGAGA1

G4 ATGCGAGAGATG\$

G5CGAGAGATG\$GAT1

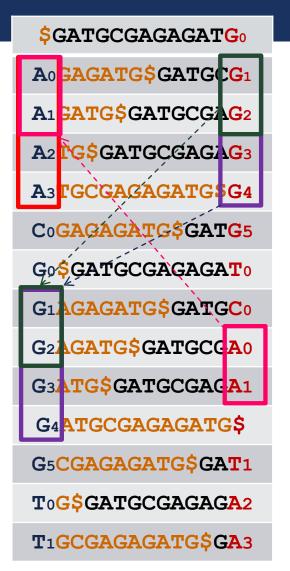
T₀G\$GATGCGAGAGA2

T₁GCGAGAGATG\$GA3

How can we use BWT of the human genome to solve the query problem?

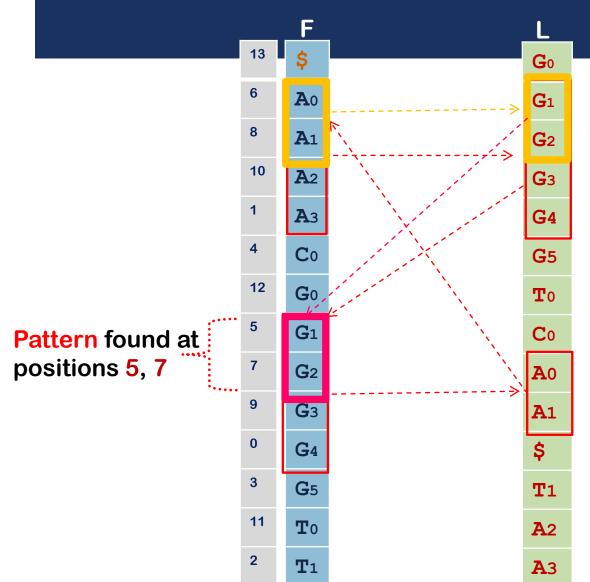


Burrows Wheeler Matrix.

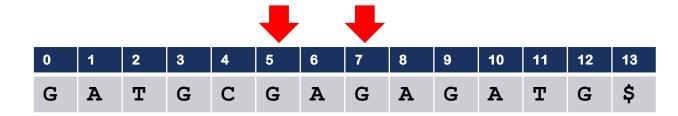


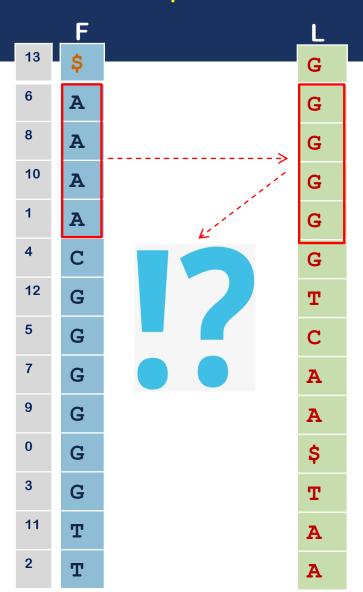
How can we use BWT of the human genome to solve the query problem?



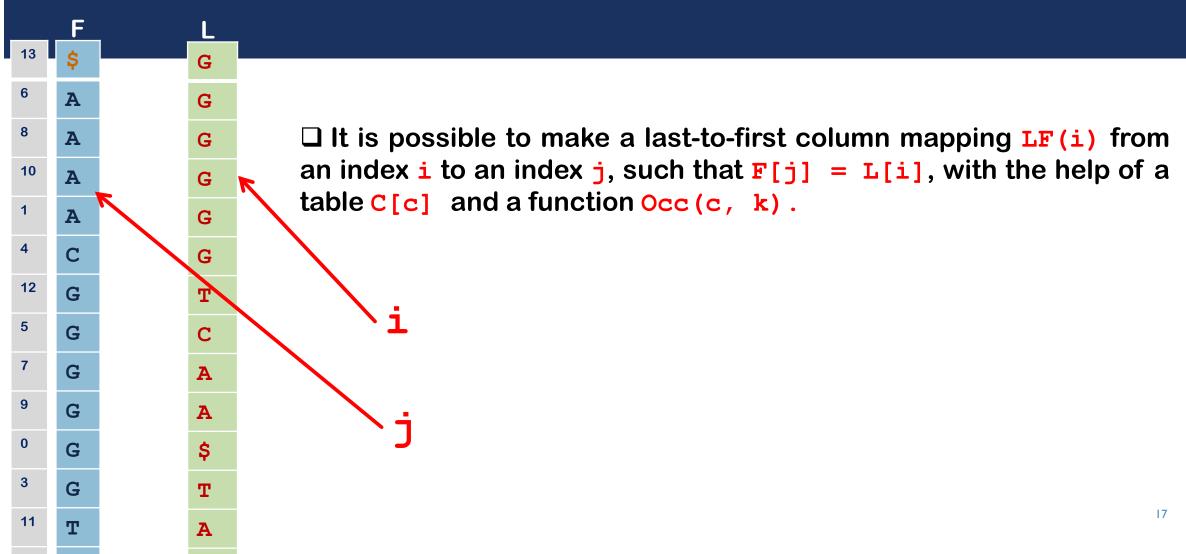




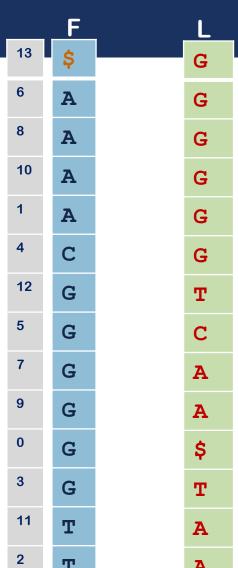








Suppose a FASTA file has a sequence GATGCGAGAGATG and the query sequence GAGA.

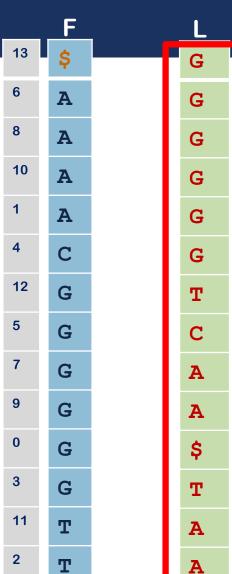


☐ Create a table C[c] that, for each character c in the alphabet, contains the number of occurrences of lexically smaller characters in the text.

✓ Step 1: Determine the text alphabet Σ .

$$\Sigma = \{\$,A,C,G,T\}$$

Suppose a FASTA file has a sequence GATGCGAGAGATG and the query sequence GAGA.

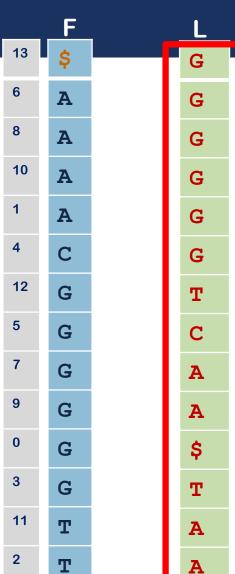


☐ Create a table C[c] that, for each character c in the alphabet, contains the number of occurrences of lexically smaller characters in the text.

$$\Sigma = \{\$,A,C,G,T\}$$

C	\$ Α	С	G	T
C[c]				

Suppose a FASTA file has a sequence GATGCGAGAGATG and the query sequence GAGA.

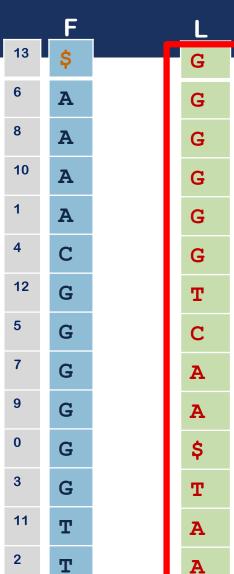


☐ Create a table C[c] that, for each character c in the alphabet, contains the number of occurrences of lexically smaller characters in the text.

$$\Sigma = \{\$,A,C,G,T\}$$

C	\$	Α	С	G	T
C[c]	0				

Suppose a FASTA file has a sequence GATGCGAGAGATG and the query sequence GAGA.

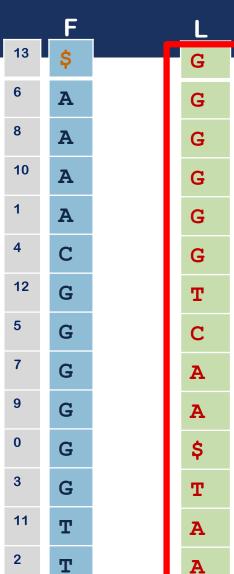


☐ Create a table C[c] that, for each character c in the alphabet, contains the number of occurrences of lexically smaller characters in the text.

$$\Sigma = \{\$,A,C,G,T\}$$

C	\$	Α	С	G	Т
C[c]	0				

Suppose a FASTA file has a sequence GATGCGAGAGATG and the query sequence GAGA.

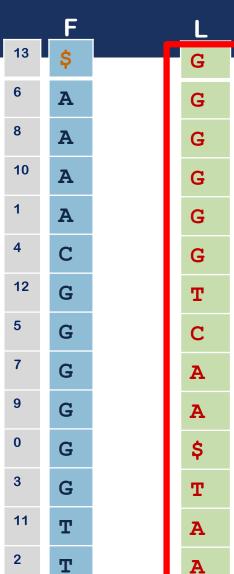


☐ Create a table C[c] that, for each character c in the alphabet, contains the number of occurrences of lexically smaller characters in the text.

$$\Sigma = \{\$,A,C,G,T\}$$

C	\$	A	С	G	Т
C[c]	0	1			

Suppose a FASTA file has a sequence GATGCGAGAGATG and the query sequence GAGA.



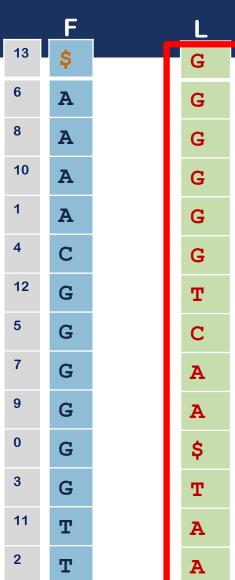
☐ Create a table C[c] that, for each character c in the alphabet, contains the number of occurrences of lexically smaller characters in the text.

$$\Sigma = \{\$,A,C,G,T\}$$

C	\$	A	С	G	T
C[c]	0	1			



Suppose a FASTA file has a sequence GATGCGAGAGATG and the query sequence GAGA.



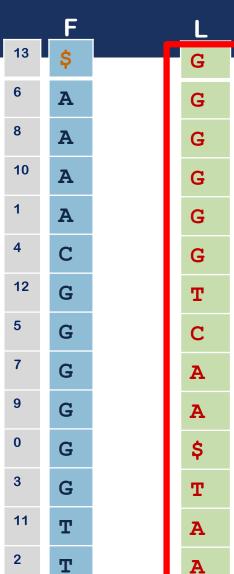
☐ Create a table C[c] that, for each character c in the alphabet, contains the number of occurrences of lexically smaller characters in the text.

$$\Sigma = \{\$,A,C,G,T\}$$

C	\$	Α	С	G	T
C[c]	0	1	5		



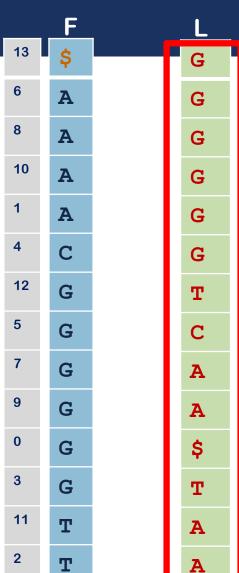
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☐ Create a table C[c] that, for each character c in the alphabet, contains the number of occurrences of lexically smaller characters in the text.

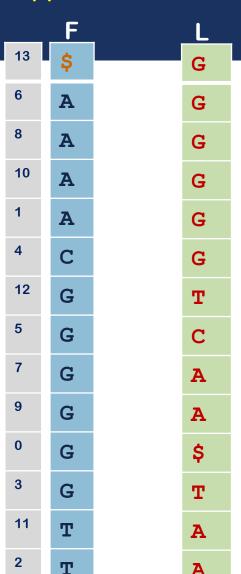
$$\Sigma = \{\$,A,C,G,T\}$$

C	\$	Α	С	G	T
C[c]	0	1	5	6	12

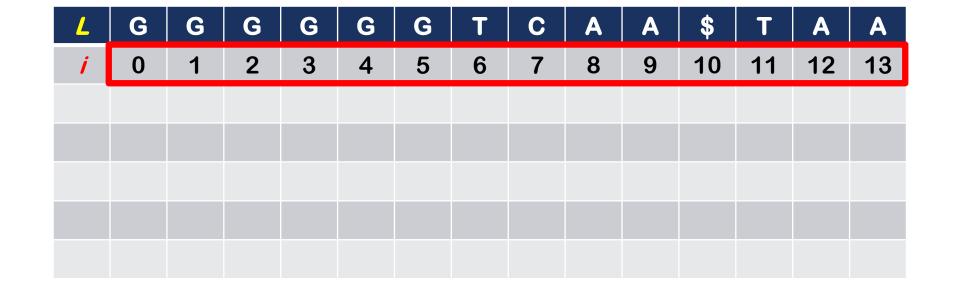


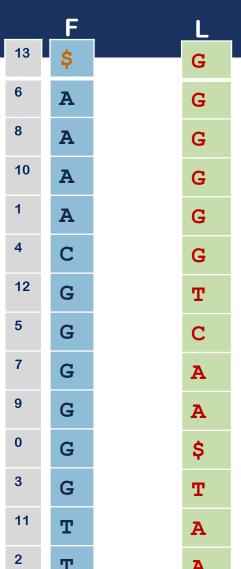
- \Box The function Occ(c, k) is the number of occurrences of character c in the prefix L[0..k].
- ✓ Step 1: Create a table that has the following attributes.

L	G	G	G	G	G	G	T	C	Α	Α	\$ T	Α	Α



- \square The function Occ(c, k) is the number of occurrences of character c in the prefix L[0..k].
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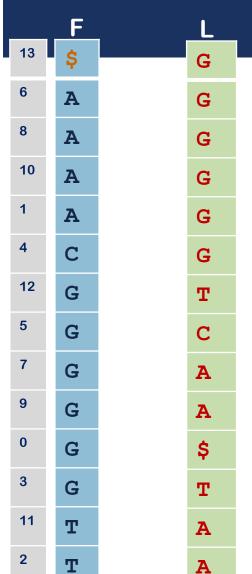




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L	G	G	G	G	G	G	T	С	Α	Α	\$	T	Α	Α
i	0	1	2	3	4	5	6	7	8	9	10	11	12	13
					- 1	A C d								

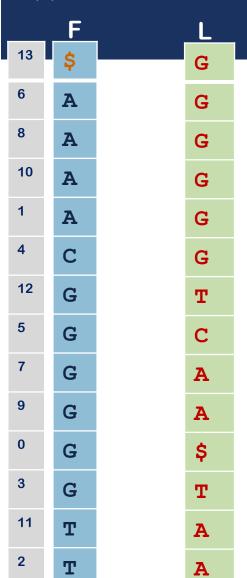
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i	0	1	2	3	4	5	6	7	8	9	10	11	12	13
\$														
Α														
C														
G														
Т														

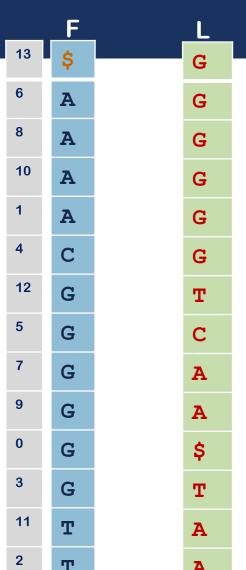
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i	0	1	2	3	4	5	6	7	8	9	10	11	12	13
\$	0													
A														
C														
G														
T														

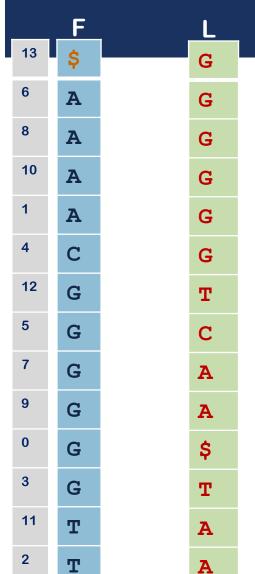
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i	0	1	2	3	4	5	6	7	8	9	10	11	12	13
\$	0	0	0	0	0	0	0	0	0	0	1	1	1	1
Α														
C														
G														
Т														

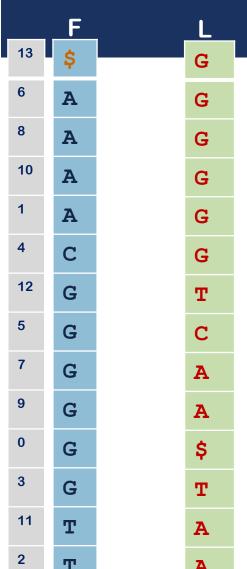
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i	0	1	2	3	4	5	6	7	8	9	10	11	12	13
\$	0	0	0	0	0	0	0	0	0	0	1	1	1	1
A	0													
C														
G														
T														

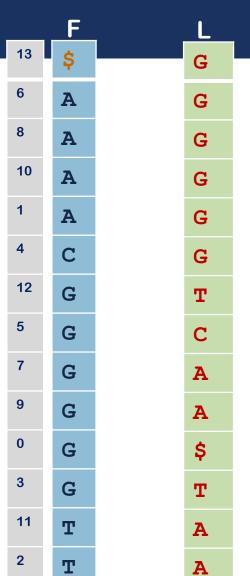
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L	G	G	G	G	G	G	T	С	A	A	\$	T	Α	Α
i	0	1	2	3	4	5	6	7	8	9	10	11	12	13
\$	0	0	0	0	0	0	0	0	0	0	1	1	1	1
Α	0	0	0	0	0	0	0	0	1	2	2	2	3	4
C														
G														
T														

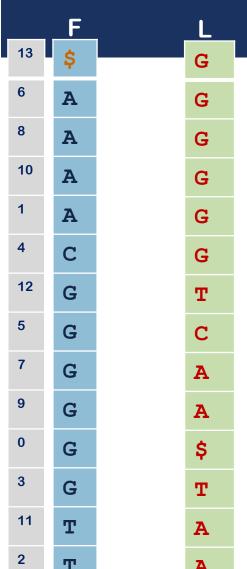
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i	0	1	2	3	4	5	6	7	8	9	10	11	12	13
\$	0	0	0	0	0	0	0	0	0	0	1	1	1	1
A	0	0	0	0	0	0	0	0	1	2	2	2	3	4
C	0													
G														
T														

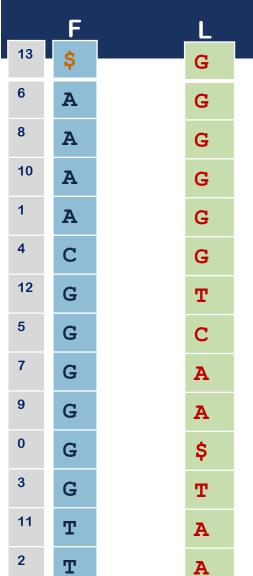
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L	G	G	G	G	G	G	T	C	Α	A	\$	Т	Α	A
i	0	1	2	3	4	5	6	7	8	9	10	11	12	13
\$	0	0	0	0	0	0	0	0	0	0	1	1	1	1
A	0	0	0	0	0	0	0	0	1	2	2	2	3	4
C	0	0	0	0	0	0	0	1	1	1	1	1	1	1
G														
T														

$$\Sigma = \{\$,A,C,G,T\}$$

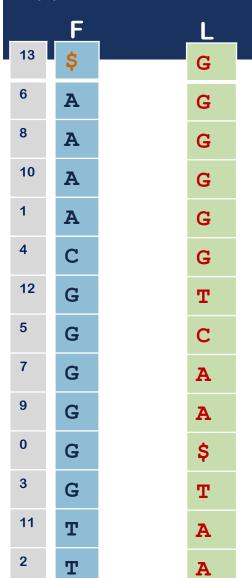


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L	G	G	G	G	G	G	T	С	A	A	\$	T	A	Α
i	0	1	2	3	4	5	6	7	8	9	10	11	12	13
\$	0	0	0	0	0	0	0	0	0	0	1	1	1	1
Α	0	0	0	0	0	0	0	0	1	2	2	2	3	4
C	0	0	0	0	0	0	0	1	1	1	1	1	1	1
G	1													
Т														

$$\Sigma = \{\$,A,C,G,T\}$$

How can we use BWT of the human genome to solve the query problem?

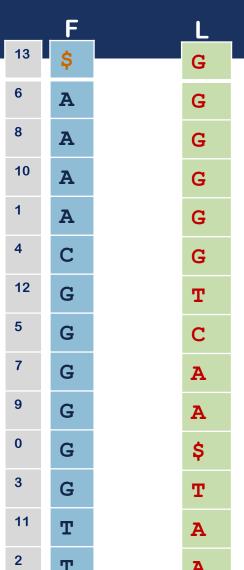


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i	0	1	2	3	4	5	6	7	8	9	10	11	12	13
\$	0	0	0	0	0	0	0	0	0	0	1	1	1	1
A	0	0	0	0	0	0	0	0	1	2	2	2	3	4
C	0	0	0	0	0	0	0	1	1	1	1	1	1	1
G	1	2	3	4	5	6	6	6	6	6	6	6	6	6
T														

$$\Sigma = \{\$,A,C,G,T\}$$

How can we use BWT of the human genome to solve the query problem?

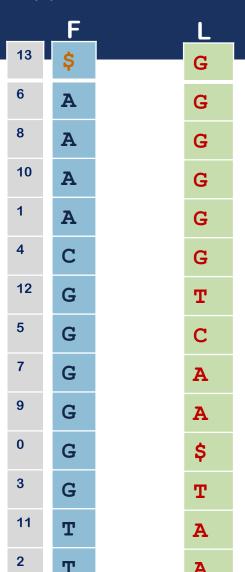


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L	G	G	G	G	G	G	T	C	Α	Α	\$	T	Α	A
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\$	0	0	0	0	0	0	0	0	0	0	1	1	1	1
A	0	0	0	0	0	0	0	0	1	2	2	2	3	4
C	0	0	0	0	0	0	0	1	1	1	1	1	1	1
G	1	2	3	4	5	6	6	6	6	6	6	6	6	6
T	0													

$$\Sigma = \{\$,A,C,G,T\}$$

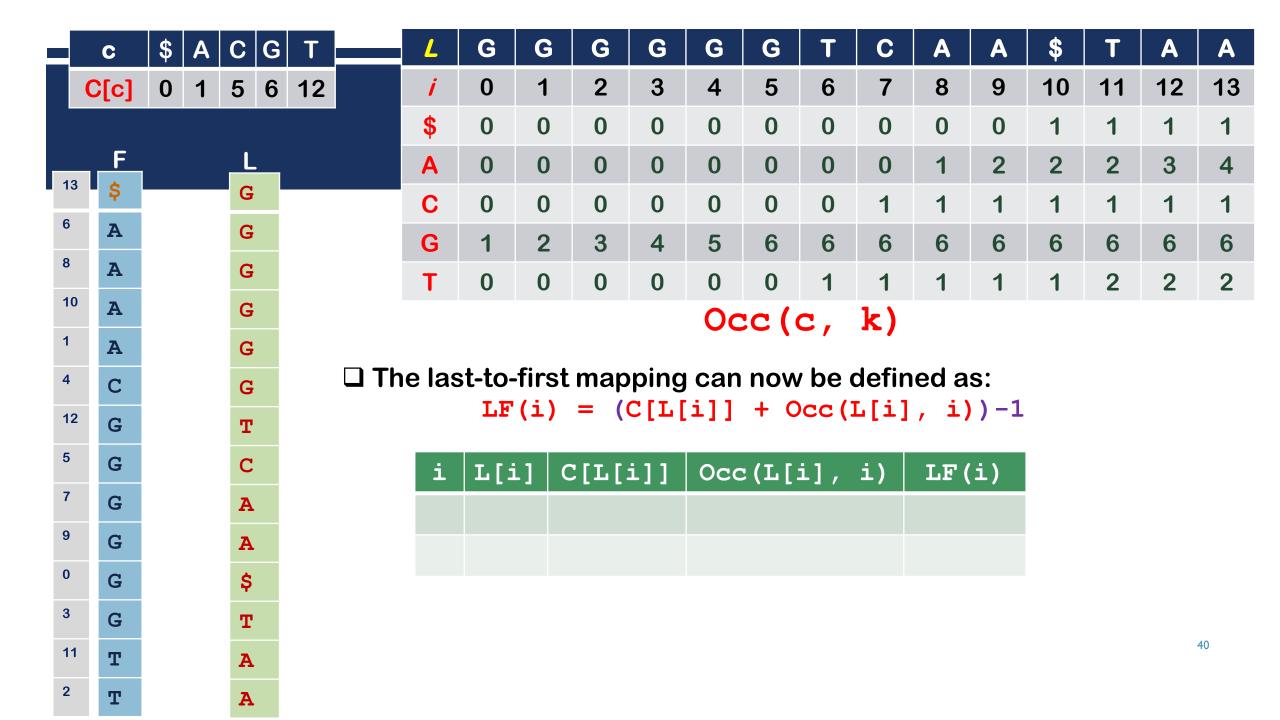
How can we use BWT of the human genome to solve the query problem?

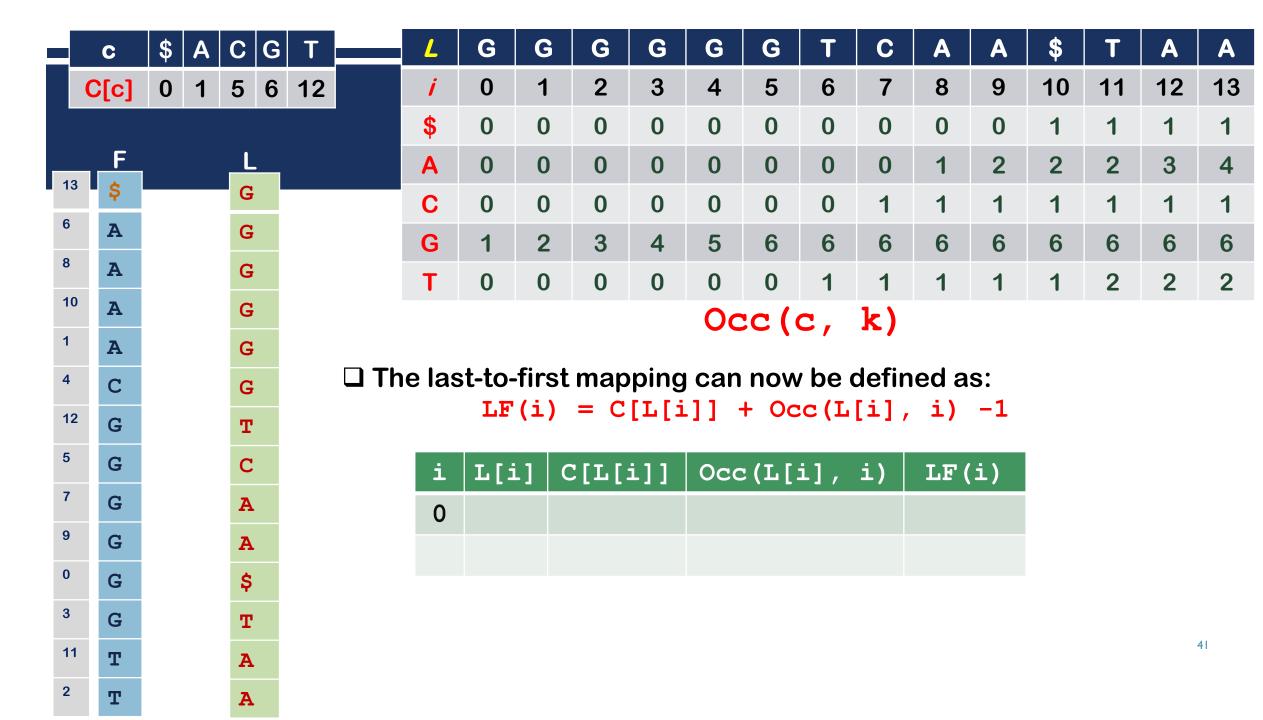


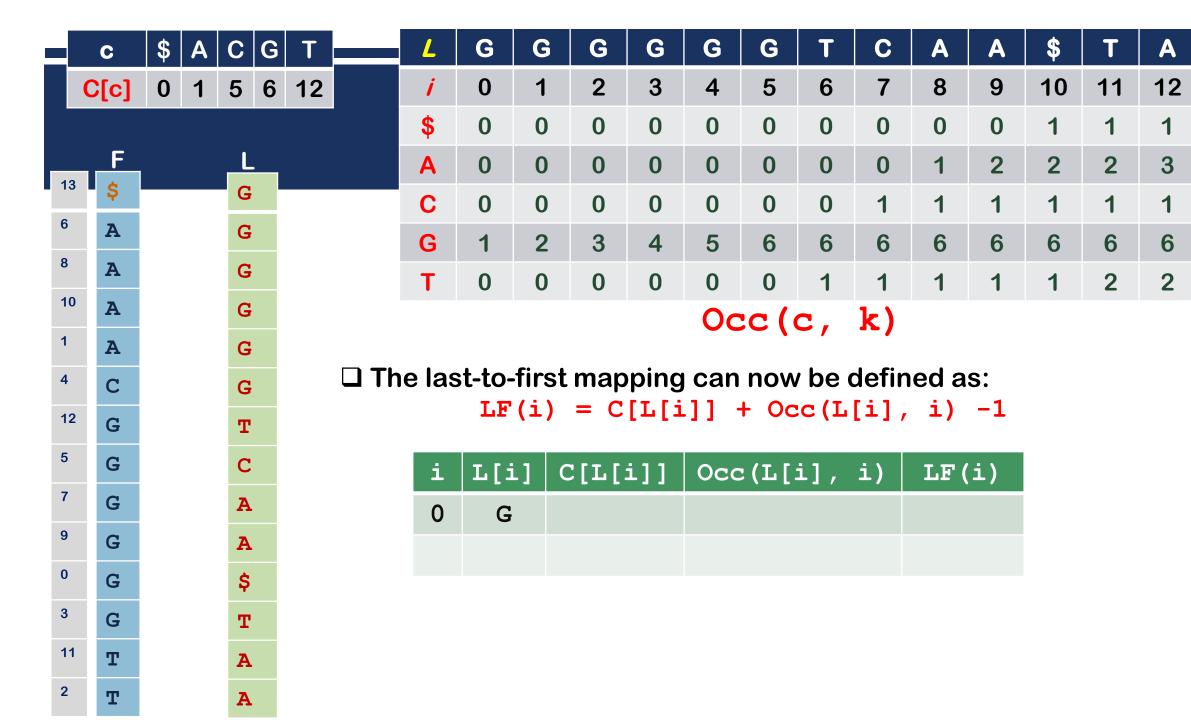
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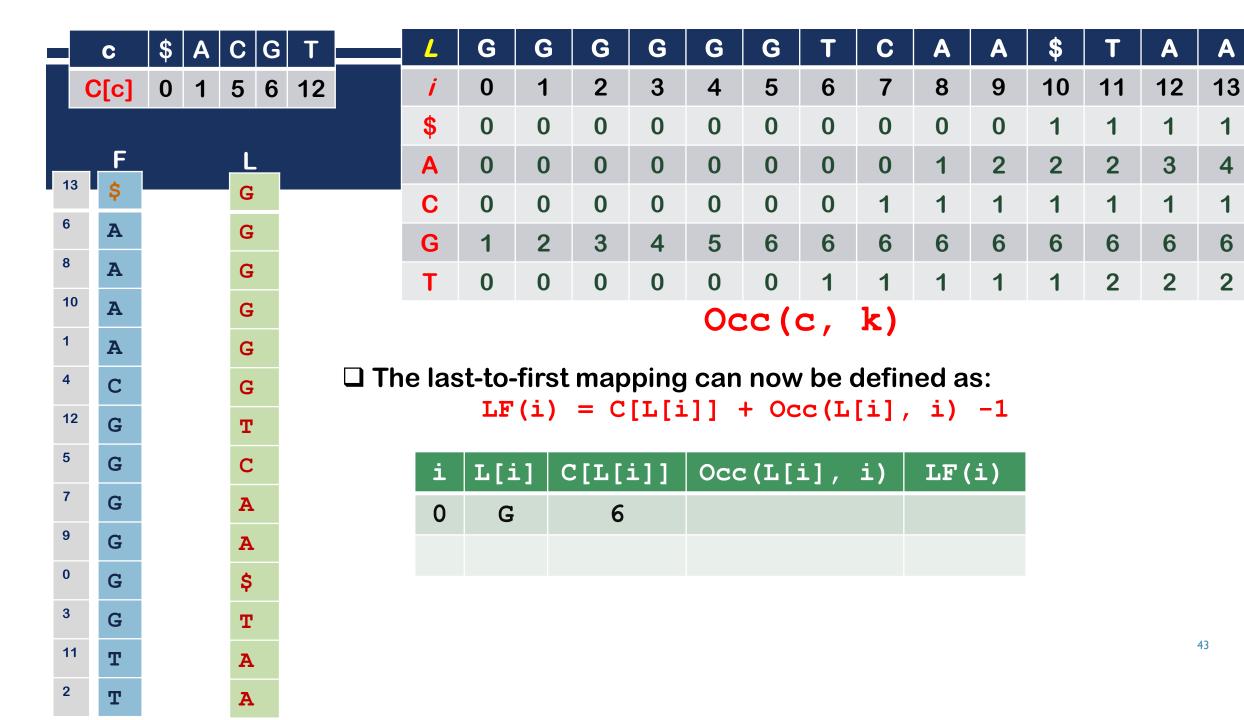
L	G	G	G	G	G	G	T	C	Α	Α	\$	T	Α	A
i	0	1	2	3	4	5	6	7	8	9	10	11	12	13
\$	0	0	0	0	0	0	0	0	0	0	1	1	1	1
A	0	0	0	0	0	0	0	0	1	2	2	2	3	4
C	0	0	0	0	0	0	0	1	1	1	1	1	1	1
G	1	2	3	4	5	6	6	6	6	6	6	6	6	6
T	0	0	0	0	0	0	1	1	1	1	1	2	2	2

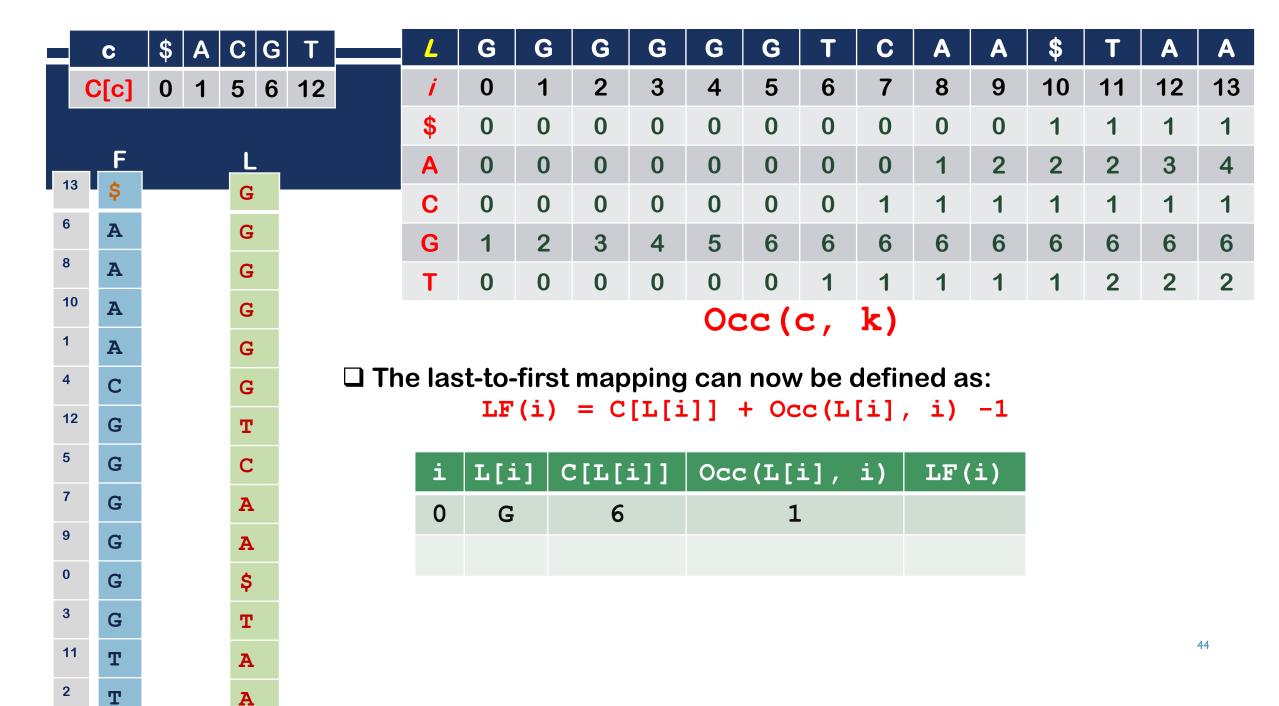
$$\Sigma = \{\$,A,C,G,T\}$$

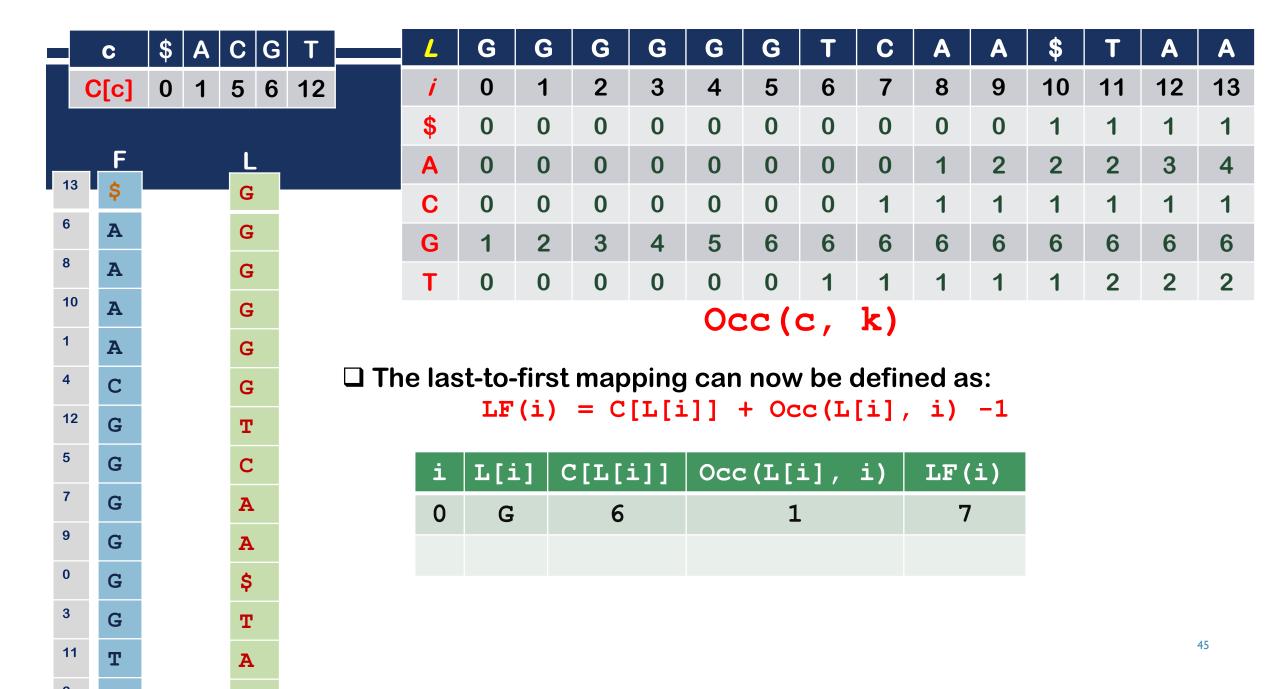


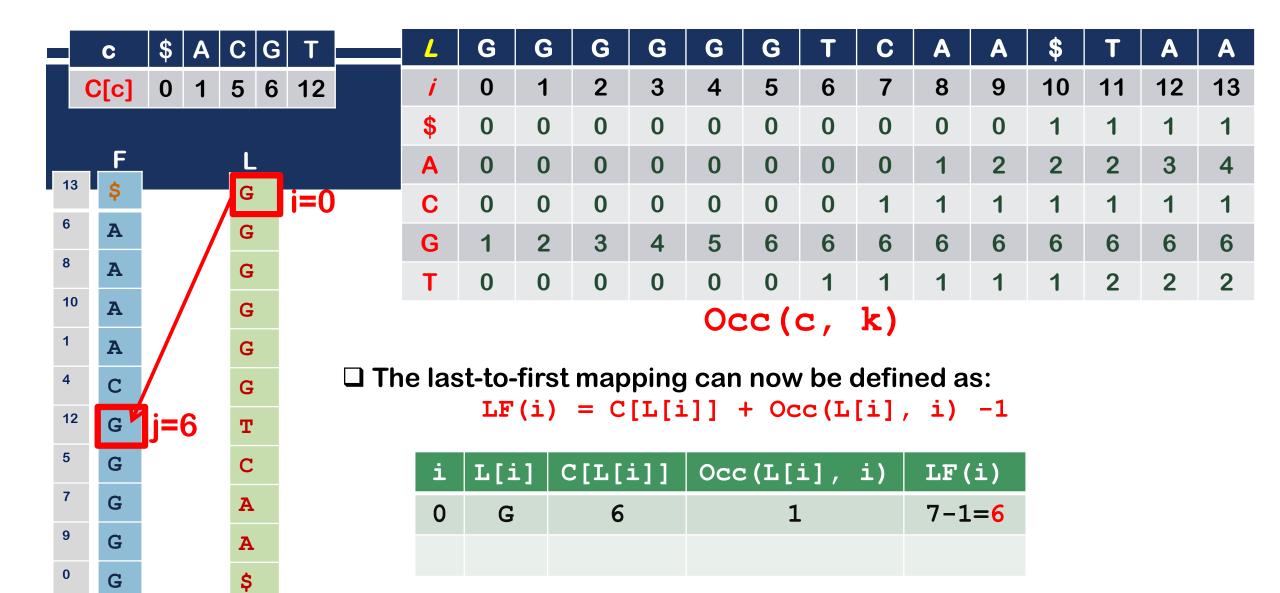












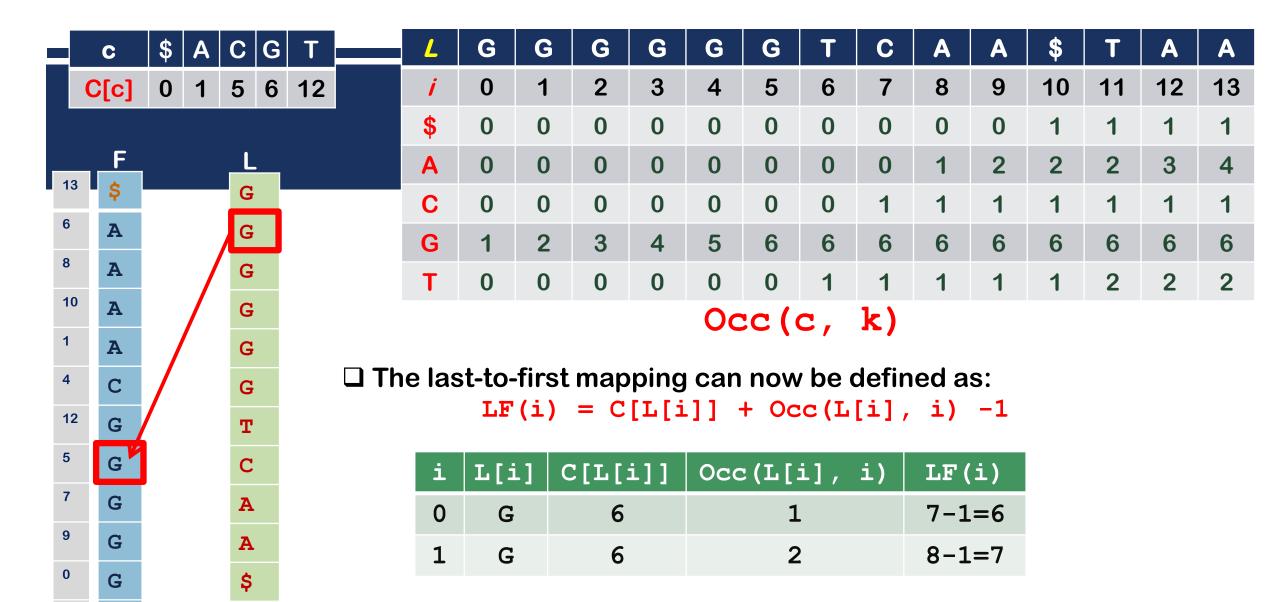
G

T

11

Т

A



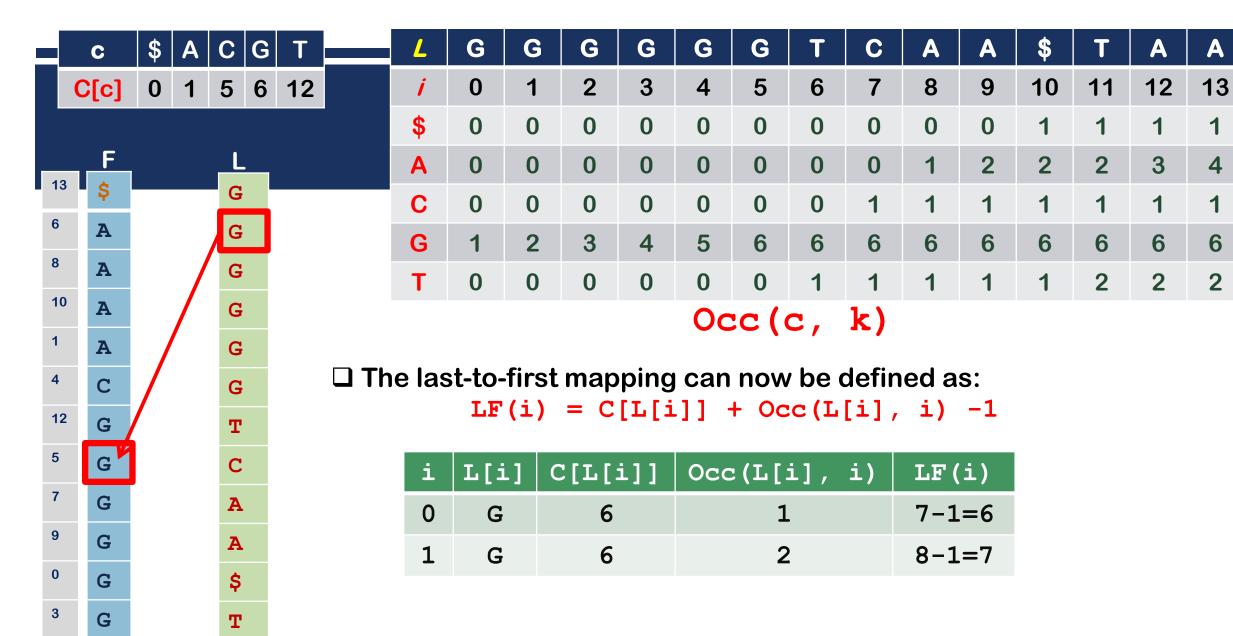
G

T

11

T

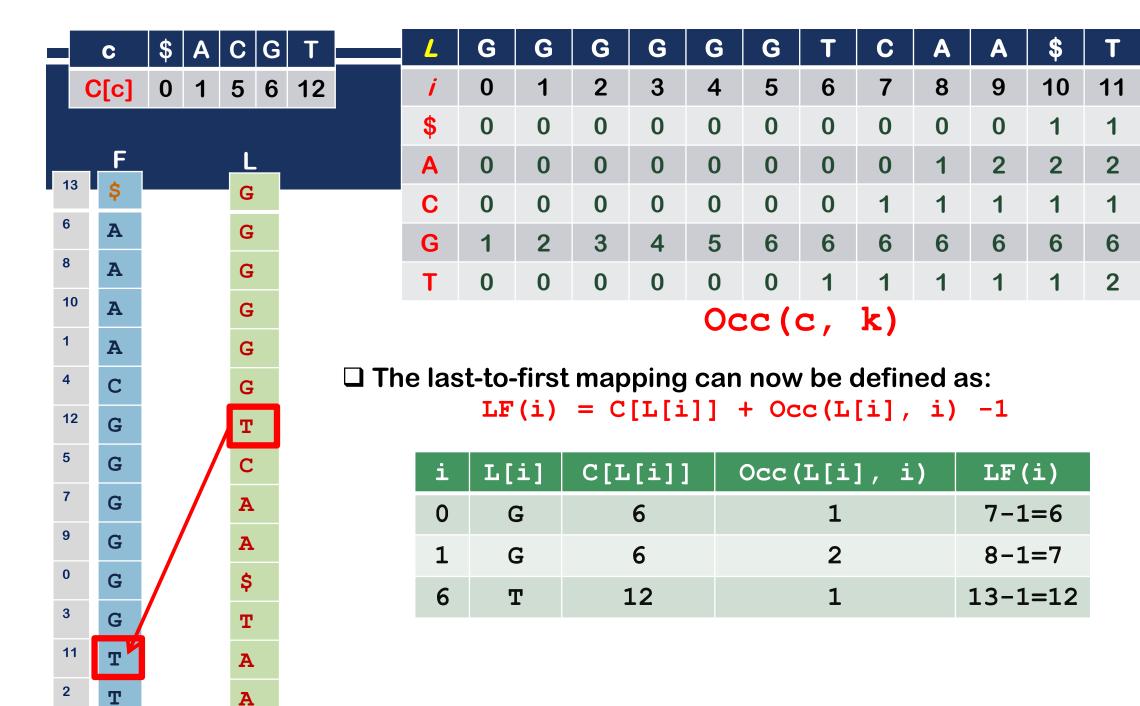
A



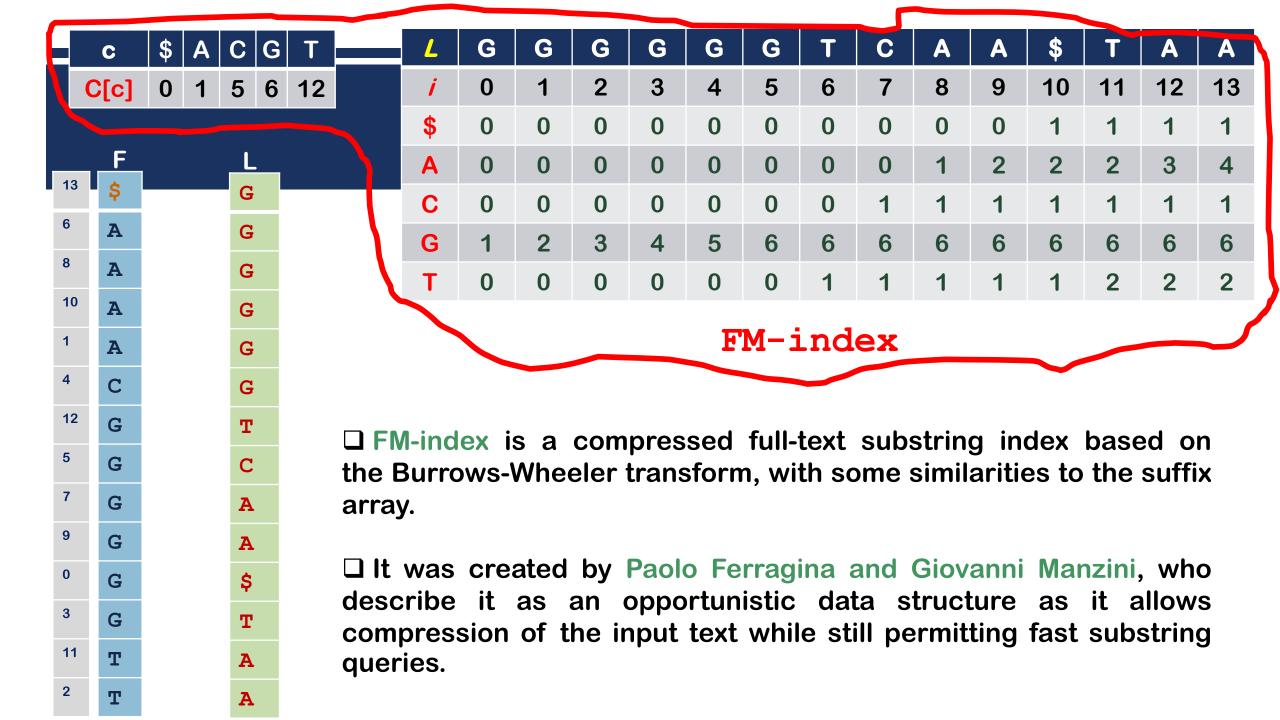
11

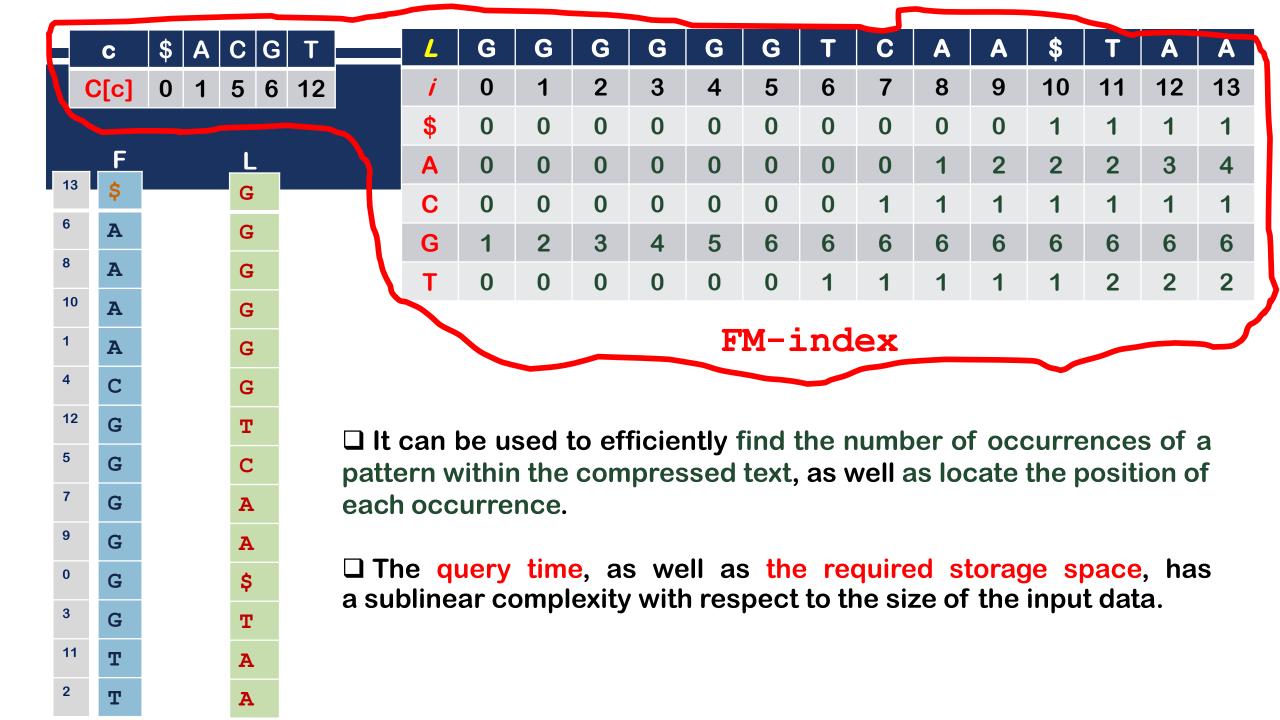
T

A



A





Suppose a FASTA file has a sequence GATGCGAGAGATG and the query sequence GAGA. G G G G G G G C A A C 12 13 C[c] 3 9 10 12 0 5 6 0 0 0 0 0 0 2 3 0 0 0 0 0 0 0 4 13 0 0 0 0 0 G A 4 6 6 6 6 6 G A 2 0 0 0 2 A G Occ(c, k)A G □ Count: The operation count takes a pattern P[1..p] and returns G the number of occurrences of that pattern in the original text T. 12 G Т 5 C **GAGA** G A A The initial range is set to [C[A]..C[A+1]-1] G \$ C[A+1]-1 C[A] [..] G T A A

Suppose a FASTA file has a sequence GATGCGAGAGATG and the query sequence GAGA. **G** G G G G G G C A A C 12 13 C[c] 3 5 9 10 12 0 4 6 11 0 0 0 0 0 0 0 2 3 0 0 0 0 0 0 0 0 4 13 0 0 0 0 0 G A 4 5 6 6 6 6 6 6 G A 2 0 0 2 0 10 G A Occ(c, k)G A □ Count: The operation count takes a pattern P[1..p] and returns C G the number of occurrences of that pattern in the original text T. 12 G Т 5 G C **GAGA** G A G A The initial range is set to [C[A]..C[A+1]-1] G \$ C[A+1]-1 C[A] [..] G T [1..4] 5-1=4A



A GAGATG\$GATGCG

A CATG\$GATGCGAG

A rg\$GATGCGAGAG

A TGCGAGAGATG\$G

CGAGAGATG\$GATG

G\$GATGCGAGAGAT

GAGAGATG\$GATGC

GAGATG\$GATGCGA

GATG\$GATGCGAGA

GATGCGAGAGATG\$

GCGAGAGATG\$GAT

TG\$GATGCGAGAGA

TGCGAGAGATG\$GA



The initial range is set to [C[A]..C[A+1]-1]

C[A]	C[A+1]-1	[]
1	5-1=4	[14]

Range of sorted suffixes that started with letter A in BWT Matrix (i.e. F column)

Suppose a FASTA file has a sequence GATGCGAGAGATG and the query sequence GAGA. G G G G G G C A A G C 3 10 12 13 C[c] 12 0 5 6 9 0 0 0 0 0 0 2 3 0 0 0 0 0 0 4 13 0 0 0 0 0 A G 4 5 6 6 6 6 G A 2 0 0 0 2 A G Occ(c, k)G A □ Count: The operation count takes a pattern P[1..p] and returns G the number of occurrences of that pattern in the original text T. 12 G T 5 C G A The new range is [C[G] + Occ(G, start-1)..C[G] + Occ(G, end)-1]A [1..4]G \$ G T C[G] Occ(G, start -1) Occ(G, end) -1A 6 Occ(G, 0) = 1Occ(G, 4) = 5 - 1 = 4[7..10]

\$GATGCGAGAGATG
AGAGATG\$GATGCG
AGATG\$GATGCGAG
ATG\$GATGCGAGAG
ATGCGAGAGATG\$G
CGAGAGATG\$GATG
G\$GATGCGAGAGAT

GA	GAGATG\$GATGC
GA	GATG\$GATGCGA
GA	<mark>rg\$</mark> gatgcgag <mark>a</mark>
GA	rgcgagagatg\$
GC	GAGAGATG\$GAT
TG	\$GATGCGAGAGA
TG	CGAGAGATG\$GA



The new range is
$$[C[G] + Occ(G, start-1)..C[G] + Occ(G, end)-1]$$

$$[1..4]$$

C[G]	Occ(G, start -1)	Occ(G, end) -1	[]
6	Occ(G,0)=1	Occ(G,4)=5-1=4	[710]

Range of sorted suffixes that started with letters GA in BWT Matrix (i.e. F column)

Suppose a FASTA file has a sequence GATGCGAGAGATG and the query sequence GAGA. G G G G G G C A A G C C[c] 3 10 12 13 12 0 4 5 6 9 0 0 0 0 0 0 0 2 3 0 0 0 0 0 0 0 4 13 0 0 0 0 0 A G 4 5 6 6 6 6 6 G 2 0 0 0 2 A G Occ(c, k)G A □ Count: The operation count takes a pattern P[1..p] and returns G the number of occurrences of that pattern in the original text T. 12 G T 5 C **GAGA** G A The new range is [C[A] + Occ(A, start-1)..C[A] + Occ(A, end)-1]A [7..10] G \$ G T C[A] Occ(A, start -1) Occ(A, end) -1A Occ(A, 10) = 2 - 1 = 11 Occ(A, 6) = 0[1..2]

\$GATGCGAGAGATG

AGAGATG\$GATGCG

AGA TG\$GATGCGAG

ATG\$GATGCGAGAG

ATGCGAGAGATG\$G

CGAGAGATG\$GATG

G\$GATGCGAGAGAT

GAGAGATG\$GATGC

GAGATG\$GATGCGA

GATG\$GATGCGAGA

GATGCGAGAGATG\$

GCGAGAGATG\$GAT

TG\$GATGCGAGAGA

TGCGAGAGATG\$GA



C[A]	Occ(A, start -1)	Occ(A, end) -1	[]
1	Occ (A, 6) =0	Occ(A,10)=2-1=1	[12]

Range of sorted suffixes that started with letters AGA in BWT Matrix (i.e. F column)

Suppose a FASTA file has a sequence GATGCGAGAGATG and the query sequence GAGA. G G G G G G C A A G C 3 10 12 13 C[c] 12 0 4 5 6 9 0 0 0 0 0 0 2 3 0 0 0 0 0 0 0 4 13 0 0 0 0 0 A G 4 5 6 6 6 6 6 G A 2 0 0 0 2 A G Occ(c, k)G A □ Count: The operation count takes a pattern P[1..p] and returns C G the number of occurrences of that pattern in the original text T. G T C **GAGA** G A G The new range is [C[G] + Occ(G, start-1)..C[G] + Occ(G, end)-1]A [1..2] G \$ G T C[G] Occ(G, start -1) Occ(G, end) -1A 6 Occ(G, 0) = 1Occ(G,2)=3-1=2[7..8]

\$GATGCGAGAGATG
AGAGATG\$GATGCG
AGATG\$GATGCGAG
ATG\$GATGCGAGAG
ATGCGAGAGATG\$G
CGAGAGATG\$GATG
G\$GATGCGAGAGAT
GAGA GATG\$GATGC
GAGA TG\$GATGCGA
GAGA TG\$GATGCGA GATG\$GATGCGAGA
GATG\$GATGCGAGA
GATG\$GATGCGAGA GATGCGAGAGATG\$



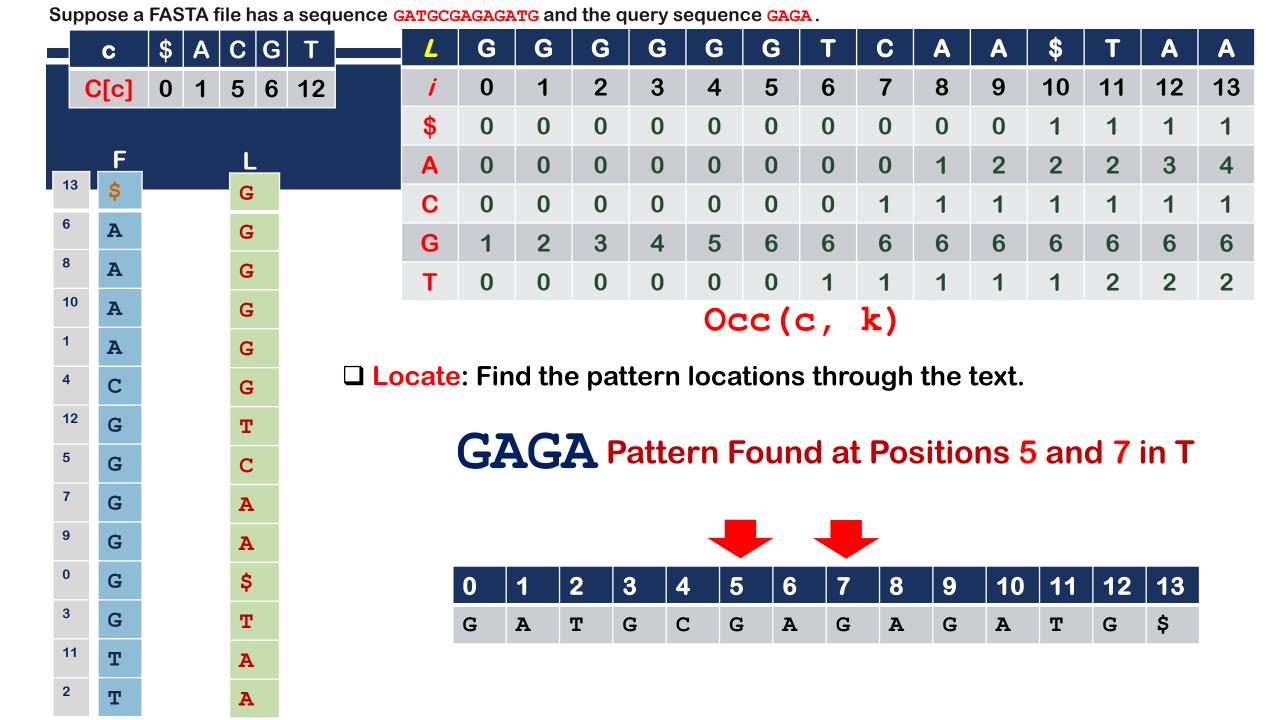
The new range is [C[G] + Occ(G, start-1)..C[G] + Occ(G, end)-1] [1..2]

C[G]	Occ(G, start -1)	Occ(G, end) -1	[]
6	Occ(G,0)=1	Occ(G,2)=3-1=2	[78]

Range of sorted suffixes that started with letters GAGA in BWT Matrix (i.e. F column)

Suppose a FASTA file has a sequence GATGCGAGAGATG and the query sequence GAGA. G G G G G G C A A 12 C[c] 3 10 13 5 6 12 0 5 6 9 0 0 0 0 0 0 3 0 0 0 0 0 0 0 0 0 0 A G 4 6 6 6 G A 2 0 0 G A Occ(c, k)G A □ Count: The operation count takes a pattern P[1..p] and returns G the number of occurrences of that pattern in the original text T. T C **GAGA** [7..8] A A The count is the same as the size of the range: 8 - 7 + 1 = 2. \$ T A

~ C			••••								u c 9	J. C. J. C	0440	000								
	C	\$	Α	С	G	T		L	G	G	G	G	G	G	T	С	A	A	\$	T	A	A
	C[c]	0	1	5	6	12		j	0	1	2	3	4	5	6	7	8	9	10	11	12	13
								\$	0	0	0	0	0	0	0	0	0	0	1	1	1	1
,	F			L	_			Α	0	0	0	0	0	0	0	0	1	2	2	2	3	4
3	\$			G				C	0	0	0	0	0	0	0	1	1	1	1	1	1	1
	A			G				G	1	2	3	4	5	6	6	6	6	6	6	6	6	6
	A			G	•			Т	0	0	0	0	0	0	1	1	1	1	1	2	2	2
	A			G	•		Occ (c, k) Locate: Find the pattern locations through the text.															
	A			G	•																	
	С			G	•		⊔ Lo	cate	: Fin	id the	e pat	tern	loca	tions	sthre	ough	the	text.				
	G			T							7		_									
	G			C	•				GF	16	A			7.	. 8]						
	G			A																		
	G			A								(7)=										
	G			\$						Lo	cate	=(8)	SA[8	sj= 7								
	G			T	ı																	
1	т			A																		
	ηı			2																		



Thank you!