Lightweight BWT Construction for Very Large String Collections

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## Whole human genome sequencing

- Modern DNA sequencing machines produce a lot of data!
  e.g. Illumina HiSeq 2000: > 40Gbases of sequence per day (paired 100-mers)
- Whole human genome sequencing: about 3Gbase genome typically sampled to 20 to 30-fold redundancy to ensure adequate coverage of both copies (i.e. each position in the genome sampled 30 times, on average)

- Datasets of 100 Gbases or more are common
- Applications: Comparing of genomes, assembl, alignment, · · ·

## The BWT

- The BWT is a reversible transformation that produces a permutation bwt(v) of an input sequence v, defined over an ordered alphabet  $\Sigma$ , so that occurrences of a given symbol tend to occur in clusters in the output sequence.
- Traditionally the major application of the Burrows-Wheeler Transform has been for Data Compression. The BWT represents for instance the heart of the BZIP2 algorithm.
- Today, there are reports of the application of the BWT in bio-informatics, full-text compressed indexes, prediction and entropy estimation, and shape analysis in computer vision, etc.

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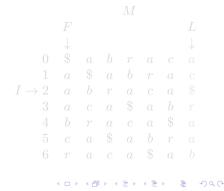
## How does BWT work?

- BWT takes as input a text v, append \$ to the end of v (\$ is unique and smaller then any other character) and produces:
  - a permutation bwt(v) of the letters of v\$.
  - the index I, that is useful in order to recover the original word v.
- Example: v = abraca
- Each row of *M* is a conjugate of *v*\$ in lexicographic order.
  - *bwt*(*v*) coincides with the last column *L* of the BW-matrix *M*.
  - The index *I* is the row of *M* containing the original sequence followed by \$.



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M

The following properties hold:

- For all  $i = 0, ..., |v|, i \neq I$ , the character F[i] follows L[i] in the original string;
- **2** for each character c, the r-th occurrence of c in F corresponds to the r-th occurrence of c in L.

Ferragina and Manzini (2000) noticed the following connection:

$$LF[i] = C[L[i]] + rank(L[i], i-1) \qquad M$$

5 c a a b r a6 r a c a a b

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instance:  
$$= 5 \text{ then } L[i] = a \text{ and}$$
  
$$I[5] = C[a] + rank(a, 4) = 1 + 2 = 3$$
  
$$I \rightarrow 2 \text{ a } b \text{ r } a \text{ c } a \text{ s } a$$
  
$$3 \text{ a } c \text{ a } \text{ s } a \text{ b } r \text{ a } c$$
  
$$3 \text{ a } c \text{ a } \text{ s } a \text{ b } r \text{ a } c$$
  
$$4 \text{ b } r \text{ a } c \text{ a } \text{ s } a \text{ b } r \text{ a } c$$
  
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LF[5]

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Ferragina and Manzini (2000) noticed the following connection:

$$LF[i] = C[L[i]] + rank(L[i], i - 1) \qquad M$$
  
For instance:  
if  $i = 5$  then  $L[i] = a$  and  
 $LF[5] = C[a] + rank(a, 4) = 1 + 2 = 3$   
$$I \rightarrow 2$$
 a b r a c a \$  
3 a c a \$ a b r a c a \$  
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## The BWT in bioinformatics

#### • BWT-based text indexes are the core of popular mapping programs

- Bowtie (Langmead et al., Genome Biology 2009)
- BWA (Li and Durbin, Bioinformatics 2009, 2010)
- SOAP2 (Li et al., Bioinformatics 2009)
- Create index from reference genome (e.g. human) create once, use many times
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- original BWT of concatenated strings
  - Straightforward to compute BWT from suffix array.
  - Lots of work on efficient linear time SA generation methods.
  - But:: need to hold SA in RAM (Simpson et al. estimate 700Gbytes) RAM for SA of 60 Gbases of data)
  - Other options:
    - Siren, SPIRE 2009: divide collection into batches, compute BWT of a each then merge
    - Ferragina et al., Latin 2010: partition string T into blocks  $T_{core}T_{b}$ , create SA of each in turn

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- without concatenating the strings belonging to S and without needing to compute their suffix array.
- incrementally via k iterations. At each of the iterations
   *j* = 1, 2, ..., k, the algorithm computes a partial BWT string bwt<sub>j</sub>(S)
   by inserting the symbols preceding the *j*-suffixes of S at their correct
   positions into bwt<sub>j-1</sub>(S). Each iteration *j* simulates the insertion of
   the *j*-suffixes in the suffix array.
- The string bwt<sub>j</sub>(S) is a 'partial BWT' in the sense that the addition of m end markers in their correct positions would make it the BWT of the collection {S<sub>1</sub>[k - j - 1, k], S<sub>2</sub>[k - j - 1, k], ..., S<sub>m</sub>[k - j - 1, k]}.
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Let  $S = \{S_1, S_2, S_3\} = \{TGCCAAC, AGAGCTC, GTCGCTT\}$  be a collection of m = 3 strings of length k = 7 on an alphabet of  $\sigma = 4$  letters.

	0	1	2	3	4	5	6	7
$S_1$								$\$_1$
$S_2$								$\$_2$
$S_3$								$\$_3$

We suppose that  $\$_1 < \$_2 < \$_3 < A < C < G < T$ .

*j*-suffix of  $S_i$  is the last j non-\$ symbols of that string and 0-suffix of  $S_i$  is  $\$_i$ .

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	0	1	2	3	4	5	6	7
$S_1$					A	A	C	$\$_1$
$S_2$					C	T	C	$\$_2$
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$S_1$			C	C	A	A	C	$\$_1$
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	0	1	2	3	4	5	6	7
$S_1$		G	C	C	A	A	C	$\$_1$
$S_2$		G	A	G	C	T	C	$\$_2$
$S_3$		T	C	G	C	T	T	$\$_3$

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	0	1	2	3	4	5	6	7
$S_1$	Т	G	C	C	A	A	C	$\$_1$
$S_2$	A	G	A	G	C	T	C	$\$_2$
$S_3$	G	Т	C	G	C	Т	Т	$\$_3$

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#### Iteration 0

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$S_1$								$\$_1$
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	0	1	2	3	4	5	6	7
$S_1$						A	C	$\$_1$
$S_2$						Т	C	$\$_2$
$S_3$						Т	Т	$\$_3$

We obtain:



Let  $S = \{S_1, S_2, S_3\} = \{TGCCAAC, AGAGCTC, GTCGCTT\}$  be a collection of m = 3 strings of length k = 7 on an alphabet of  $\sigma = 4$  letters.

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$S_2$						T	C	$\$_2$
$S_3$						T	Т	$\$_3$

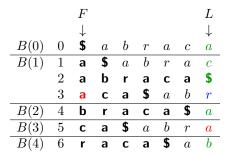
We obtain:



# Observation

$$LF[i] = C[L[i]] + rank(L[i], i-1) \\$$

We can think of bwt<sub>i</sub>(S) as being partitioned into  $\sigma + 1$  strings  $B_i(0), B_i(1), \ldots, B_i(\sigma)$ , with the symbols in  $B_i(h)$  being those that are associated with the suffixes of S that are of length i or less and begin with  $c_0 =$  and  $c_h \in \Sigma$ , for  $h = 1, \ldots, \sigma$ .

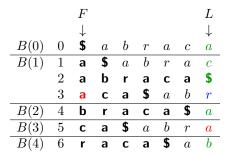


in  $\sigma + 1$  external files that are sequentially read one-by some  $\sigma_{\sigma}$ ,  $\sigma_{\sigma}$ ,

# Observation

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We can think of bwt<sub>i</sub>(S) as being partitioned into  $\sigma + 1$  strings  $B_i(0), B_i(1), \ldots, B_i(\sigma)$ , with the symbols in  $B_i(h)$  being those that are associated with the suffixes of S that are of length j or less and begin with  $c_0 =$  and  $c_h \in \Sigma$ , for  $h = 1, \ldots, \sigma$ .

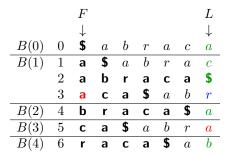


### We do not need the array C. We only need the rank function.

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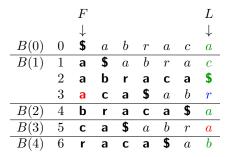


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# Observation

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We do not need the array C. We only need the rank function. We note that  $B_i(0)$  is constant for all j and, at each iteration j, we store  $B_i(h)$ in  $\sigma + 1$  external files that are sequentially read one-by-one. The sequence of  $\sigma + 1$  external files that are sequentially read one-by-one. The sequence of  $\sigma + 1$  external files that are sequentially read one-by-one. The sequence of  $\sigma + 1$  external files that are sequentially read one-by-one. The sequence of  $\sigma + 1$  external files that are sequentially read one-by-one. The sequence of  $\sigma + 1$  external files that are sequentially read one-by-one. The sequence of  $\sigma + 1$  external files that are sequentially read one-by-one. The sequence of  $\sigma + 1$  external files that are sequence of

# Looking in detail at iteration 6

	- C					
	$B_{5}(0)$	Associated Suffixes	$TGCCAAC\$_1$ ,		$B_{6}(0)$	Associated Suffixes
0	C	\$ <sub>1</sub>	$AGAGCTC\$_2$ ,	0	C	\$ <sub>1</sub>
1	C	\$ <sub>2</sub>	$GTCGCTT\$_3$ .	1	C	\$ <sub>2</sub>
2	T	\$3		2	T	\$3
		-	$P_5(0) = [], N_5(0) = [](empty array)$			-
	$B_{5}(1)$	Associated Suffixes	$P_5(1) = [2], N_5(1) = [2]$		$B_{6}(1)$	Associated Suffixes
0	C	$AAC\$_1$	$P_5(2) = [3, 4], N_5(2) = [1, 3]$	0	C	$AAC\$_1$
1	A	$AC\$_1$	$P_5(3) = [], N_5(3) = []$	1	A	AC <sup>\$1</sup>
2	G	AGCTC\$2	$P_5(4) = [], N_5(4) = []$	2	G	AGCTC <sup>\$2</sup>
	$B_{5}(2)$	Associated Suffixes			$B_{6}(2)$	Associated Suffixes
0	A	$C\$_1$		0	A	$C\$_1$
1	T	$C\$_{2}$	For $h = 0, 3, 4$ : nothing	1	T	$C_{2}^{*}$
2	C	$CAAC\$_1$	For $h = 1$ :	2	C	$CAAC\$_1$
3	G	CCAAC\$1	rank(G, 2) = 0(sequence = 2)	3	G	CCAAC <sup>\$1</sup>
4	т	CGCTT\$3	For $h = 2$ :	4	T	$CGCTT\$_3$
5	G	$CTC\$_2$	rank(G, 3) = 1(sequence = 1)	5	G	$CTC\$_2$
6	$\overline{G}$	$CTT\$_3$	rank(T, 4) = 2(sequence = 3)	6	$\overline{G}$	$CTT\$_3$
		3	(,,) (-1			3
	$B_{5}(3)$	Associated Suffixes	$T$ GCCAAC $\$_1$ ,		$B_{6}(3)$	Associated Suffixes
0	A	GCTC <sup>\$2</sup>	$A$ GAGCTC $\$_2$ ,	0	Α	GAGCTC\$2
1	C	$GCTT\$_3$	GTCGCTT\$3.	1	т	GCCAAC <sup>\$1</sup>
		0	0	2	A	GCTC\$2
			↓	3	C	$GCTT\$_3$
			*			
	$B_{5}(4)$	Associated Suffixes	$P_6(0) = [], N_6(0) = []$		$B_{6}(4)$	Associated Suffixes
0	T	$T\$_{3}$	$P_6(1) = [], N_6(1) = []$	0	T	$T\$_{3}$
ĩ	$\hat{C}$	$TC\$_2$	$P_6(2) = [], N_6(2) = []$	ĭ	$\hat{C}$	$TC\$_2$
2	$\tilde{C}$	$TT_{3}^{10,02}$	$P_6(3) = [0, 1]$ and $N_6(3) = [2, 1]$	2	G	TCGCTT\$3
2	0	+0	$P_6(4) = [2]$ and $N_6(4) = [3]$	3	$\overline{C}$	$TT\$_3$
			10(4) - [-] and $10(4) - [0]$	0	0	1 1 43

Position of GCCAAC<sup>\$1</sup> in G segment = # of G before CCAAC<sup>\$1</sup> in partial BWT = # of G in \$-segment +# of G in

A-segment +# of G before CCAAC<sup>1</sup> in C-segment

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# Looking in detail at iteration 6

	<b>O</b>					
	$B_{5}(0)$	Associated Suffixes	$T \mathbf{G} \mathbf{CCAAC} \$_1,$		$B_{6}(0)$	Associated Suffixes
0	C	\$ <sub>1</sub>	$AGAGCTC\$_2$ ,	0	C	\$ <sub>1</sub>
1	C	\$ <sub>2</sub>	GTCGCTT\$3.	1	C	\$ <sub>2</sub>
2	T	\$ <sub>3</sub>		2	T	\$3
			$P_5(0) = [], N_5(0) = [](empty array)$			
	$B_{5}(1)$	Associated Suffixes	$P_5(1) = [2], N_5(1) = [2]$		$B_{6}(1)$	Associated Suffixes
0	C	$AAC\$_1$	$P_5(2) = [3, 4], N_5(2) = [1, 3]$	0	C	$AAC\$_1$
1	A	$AC\$_1$	$P_5(3) = [], N_5(3) = []$	1	A	$AC\$_1$
2	G	AGCTC\$-	$P_5(4) = [], N_5(4) = []$	2	G	AGCTC\$2
		2				2
	$B_{5}(2)$	Associated Suffixes	↓		$B_{6}(2)$	Associated Suffixes
0	A	$C\$_{1}$	·	0	A	C\$1
1	T	$C\$_2$	For $h = 0, 3, 4$ : nothing	1	T	$C\$_2$
2	C	CAAC <sup>1</sup>	For $h = 1$ :	2	C	CAAC <sup>1</sup>
3	G	CCAAC\$1	rank(G, 2) = 0(sequence = 2)	3	G	$CCAAC\$_1$
4	Ť	CGCTT\$3	For $h = 2$ :	4	$\tilde{T}$	$CGCTT\$_3$
5	G	$CTC\$_2$	rank(G,3) = 1(sequence = 1)	5	G	$CTC\$_2$
6	G	$CTT\$_3$	rank(T, 4) = 2(sequence = 3)	6	G	$CTT\$_3$
0	G	01103	Tann(1, 4) = 2(sequence = 0)	0	G	01103
	$B_{5}(3)$	Associated Suffixes	$T$ GCCAAC $\$_1$ ,		$B_{6}(3)$	Associated Suffixes
0	A	$GCTC\$_2$	AGAGCTC <sup>1</sup> ,	0	_0(≎) A	GAGCTC\$2
1	C	$GCTT\$_3$	GTCGCTT\$3.	1	т	GCCAAC\$1
-	0	001103	0.0001.03.	2	À	GCTC\$2
			$\Downarrow$	3	$\tilde{C}$	$GCTT\$_3$
			v	0	U	001103
	$B_{5}(4)$	Associated Suffixes	$P_6(0) = [], N_6(0) = []$		$B_{6}(4)$	Associated Suffixes
0	T T	$T\$_3$	$P_6(1) = [], N_6(1) = []$	0	T T	$T\$_3$
1	Ċ	$TC_{2}^{T}$	$P_6(1) = [], N_6(1) = []$ $P_6(2) = [], N_6(2) = []$	1	$\hat{C}$	$TC\$_{2}$
2	C	$TT\$_{3}$	$P_6(2) = [1, N_6(2) = [1]$ $P_6(3) = [0, 1]$ and $N_6(3) = [2, 1]$	2	G	TCGCTT\$3
2	U	1 1 03		3	C	
			$P_6(4) = [2] \text{ and } N_6(4) = [3]$	3	C	$TT\$_{3}$

Position of GCCAAC<sup>\$1</sup> in G segment = # of G before CCAAC<sup>\$1</sup> in partial BWT = # of G in \$-segment +# of G in

A-segment +# of G before  $CCAAC\$_1$  in C-segment

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# Two versions of our algorithm: BCR vs. BCRext

	BCR	BCRext
CPU time	O(ksort(m))	O(km)
RAM usage (bits)	$O((m + \sigma^2)log(mk))$	$O(\sigma^2 log(mk))$
I/O (bits)	$O(mk^2log(s))$	$O(mk^2log(\sigma))$
	(partial BWT)	(partial BWT)
	$O(mklog(\sigma))$	$O(mk^2log(\sigma))$
	(sequence slices)	(sequences)
		O(mklog(mk))
		(P - array)
		O(mklog(m))
		(N - array)

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# Performance on human DNA sequence data

Dataset size	Program	Wallclock time	CPU	Max RAM
(millions of 100-mers)	Program	(µs per input base)	efficiency (%)	(Gbyte)
85	bwte	7.99	99	4.00
	rlcsa	2.44	99	13.40
	BCR	1.01	83	1.10
	BCRext	4.75	27	negligible
1000	BCR	5.74	19	13.00
	BCRext	5.89	21	negligible

# Further works

- Able to compute BWT of 1 billion 100-mers in under 24 hours
- Ongoing work:
  - Further optimizations to construction, parallelization
  - Software library for construction/querying of BWT of large string collections
  - Algorithm can be adapted to allow sets of strings to be added/removed from collection

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• Applications of BWT of string collection to bioinformatics