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: $>40{\rm Gbases}$ 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 Σ , 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 \$.



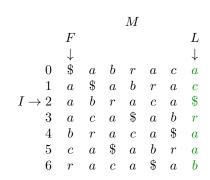
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The following properties hold:

- For all $i=0,\ldots,|v|,\ i\neq I$, 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.

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

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

$$F \qquad \qquad \bot$$
For instance:
$$0 \quad \$ \quad a \quad b \quad r \quad a \quad c \quad a$$

$$1 \quad a \quad \$ \quad a \quad b \quad r \quad a \quad c$$

$$LF[5] = C[a] + rank(a, 4) = 1 + 2 = 3$$

$$I \rightarrow 2 \quad a \quad b \quad r \quad a \quad c \quad a \quad \$$$

$$3 \quad a \quad c \quad a \quad \$ \quad a \quad b \quad r$$

$$4 \quad b \quad r \quad a \quad c \quad a \quad \$ \quad a$$

$$5 \quad c \quad a \quad \$ \quad a \quad b \quad r \quad a$$

$$6 \quad c \quad a \quad \$ \quad a \quad b \quad r \quad a$$

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- BWT-based text indexes are the core of popular mapping programs
 - Bowtie (Langmead et al., Genome Biology 2009)
 - ② 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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Let S be a collection of m strings of length k on an alphabet of σ letters.

Our algorithm computes the BWT of S

- without concatenating the strings belonging to S and without needing to compute their suffix array.
- incrementally via k iterations. At each of the iterations $j=1,2,\ldots,k$, the algorithm computes a partial BWT string bwt $_{j}(S)$ by inserting the symbols preceding the j-suffixes of S at their correct positions into $\mathrm{bwt}_{j-1}(S)$. Each iteration j simulates the insertion of the j-suffixes in the suffix array.
- The string $\operatorname{bwt}_j(S)$ 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 $\{S_1[k-j-1,k],S_2[k-j-1,k],\ldots,S_m[k-j-1,k]\}$.
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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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Iteration 0

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

We can think of $\mathrm{bwt}_j(\mathsf{S})$ as being partitioned into $\sigma+1$ strings $B_j(0), B_j(1), \ldots, B_j(\sigma)$, with the symbols in $B_j(h)$ 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 $h=1,\ldots,\sigma$.

		F						L
		\downarrow						\downarrow
B(0)	0	\$	a	b	r	a	c	a
B(1)	1	a	\$	\overline{a}	b	r	\overline{a}	\overline{c}
	2	a	b	r	a	С	a	\$
	3	a	C	а	\$	a	b	r
B(2)	4	b	r	а	С	a	\$	\overline{a}
B(3)	5	С	а	\$	a	b	r	\overline{a}
B(4)	6	r	a	С	а	\$	\overline{a}	\overline{b}

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

We note that $B_j(0)$ is constant for all j and, at each iteration j, we store $B_j(h)$ in $\sigma+1$ external files that are sequentially read one-by-one- σ

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Looking in detail at iteration 6

	• • • • • •					
	$B_{5}(0)$	Associated Suffixes	T G CCAAC $\$_1$,		$B_6(0)$	Associated Suffixes
0	C	\$1	$A_{\mathbf{G}}^{\mathbf{G}}\mathbf{AGCTC}\$_{2}$,	0	C	\$1
1	C	\$2	$G_{\mathbf{T}}^{\mathbf{T}}CGCTT_{3}^{\mathbf{T}}$.	1	C	\$2
2	T	\$3	ŭ	2	T	\$3
		ŭ .	$P_5(0) = [], N_5(0) = []$ (empty array)			o .
	$B_{5}(1)$	Associated Suffixes	$P_5(1) = [2], N_5(1) = [2]$		$B_6(1)$	Associated Suffixes
0	$\stackrel{\circ}{C}$	$AAC\$_1$	$P_5(2) = [3, 4], N_5(2) = [1, 3]$	0	$\stackrel{\circ}{C}$	$AAC\$_1$
1	A	$AC\$_1$	$P_5(3) = [], N_5(3) = []$	1	A	$AC\$_1$
2	G	AGCTC\$2	$P_5(4) = [], N_5(4) = []$	2	G	$\overrightarrow{AGCTC}\$_2$
		-	0() 8. 0() 8			-
	$B_{5}(2)$	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	$CCAAC$ $\$_1$
4	T	CGCTT\$3	For $h = 2$:	4	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	$CTT\$_3$
		Ü	* * * * * * * * * * * * * * * * * * * *			o .
	$B_{5}(3)$	Associated Suffixes	T GCCAAC $\$_1$,		$B_6(3)$	Associated Suffixes
0	$\stackrel{\sim}{A}$	$GCTC\$_2$	A GAGCTC $\$_2$,	0	A	$GAGCTC\$_2$
1	C	$GCTT\$_3$	GTCGCTT\$3.	1	T	GCCAAC\$1
		o o	· ·	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
1	C	$TC\$_2$	$P_6(2) = [], N_6(2) = []$	1	C	$TC\$_2$
2	C	$TT\$_3^2$	$P_6(3) = [0,1]$ and $N_6(3) = [2,1]$	2		TCGCTT\$3
		. 0	$P_6(4) = [2]$ and $N_6(4) = [3]$	3	C	$TT\$_3$
			3() [] 0(-) [-]	-	-	. 0

Position of $GCCAAC\$_1$ in G segment =# of G before $CCAAC\$_1$ in partial BWT =# of G in \$-segment +# of G in

Looking in detail at iteration 6

	٥	actan	at 1001 at 1011 0			
	$B_5(0)$	Associated Suffixes	$T_{\mathbf{G}}^{\mathbf{GCCAAC}}$,		$B_6(0)$	Associated Suffixes
0	$\stackrel{\sim}{C}$	\$1	$A_{\mathbf{G}}^{\mathbf{G}}AGCTC\$_{2}$	0	\overrightarrow{C}	\$1
1	C	\$2	GT CGCTT $\$_3$.	1	C	\$2
2	T	\$3	ŭ	2	T	\$3
		. 0	$P_5(0) = [], N_5(0) = []$ (empty array)			. 3
	$B_{5}(1)$	Associated Suffixes	$P_5(1) = [2], N_5(1) = [2]$		$B_6(1)$	Associated Suffixes
0	Ĉ	$AAC\$_1$	$P_5(2) = [3, 4], N_5(2) = [1, 3]$	0	$\stackrel{\circ}{C}$	$AAC\$_1$
1	A	$AC\$_1$	$P_5(3) = [], N_5(3) = []$	1	A	$AC\$_1$
2	G	AGCTC\$2	$P_5(4) = [], N_5(4) = []$	2	G	\overrightarrow{AGCTC} \$2
			0() [] 0() []			2
	$B_{5}(2)$	Associated Suffixes			$B_6(2)$	Associated Suffixes
0	À	C\$1		0	À	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	$CCAAC\$_1$
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	G	$CTT\$_3$	rank(T, 4) = 2(sequence = 3)	6	G	$CTT\$_3$
		3	, , , , , , , , , , , , , , , , , , , ,			0
	$B_{5}(3)$	Associated Suffixes	T GCCAAC $\$_1$,		$B_6(3)$	Associated Suffixes
0	À	$GCTC\$_2$	$AGAGCTC\$_2$	0	A	$GAGCTC\$_2$
1	C	$GCTT\$_3$	GTCGCTT\$3.	1	T	GCCAAC\$1
		· ·	· ·	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
1	C	$TC\$_2$	$P_6(2) = [], N_6(2) = []$	1	C	$TC\$_2$
2	C	$TT\$_3$	$P_6(3) = [0, 1] \text{ and } N_6(3) = [2, 1]$	2	G	TCGCTT $\$_3$
		•	$P_6(4) = [2] \text{ and } N_6(4) = [3]$	3	C	$TT\$_3$
			0() []=0(-) [[0]			. 0

 $\text{Position of } GCCAAC\$_1 \text{ in } G \text{ segment} = \# \text{ of } G \text{ before } CCAAC\$_1 \text{ in partial BWT} = \# \text{ of } G \text{ in \$-segment} + \# \text{ of } G \text{ in$

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)

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
 - Applications of BWT of string collection to bioinformatics