Lecture Notes in Computer Science: Authors' Instructions for the Preparation of Camera-Ready Contributions to LNCS/LNAI/LNBI Proceedings

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Abstract. The abstract should summarize the contents of the paper and should contain at least 70 and at most 150 words. It should be written using the *abstract* environment.

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1 Background: Compressed Text Indexes

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Burrows-Wheeler Transform. The Burrows-Wheeler Transform of a string is a reversible permutation of its characters that was originally developed for compression because it tends to cluster together identical symbols, so it can be efficiently stored with techniques such as run-length encoding or move-to-front coding. More recently, it has been applied to full-text indexing because it allows the search of a substring in large texts in linear time with respect to the length of the substring, with a small memory footprint. The BWT of a string $T = t_1t_2 \ldots t_n$ is constructed by sorting its n cyclic shifts $t_1t_2 \ldots t_n$, $t_2 \ldots t_nt_1$, $\ldots$, $t_nt_1 \ldots t_{n-1}$ in lexicographic order. The matrix obtained is called the Burrows-Wheeler matrix and the sequence from its last column is the BWT. An example is given below. The last character t_n is always a unique terminating symbol $ that is lexicographically smaller than all the symbols in T and is essential for decoding. Storing the first and last column of the BWM is sufficient for finding the number of exact matches of a query in T. For locating the position of the matches in T an additional data structure is required, the suffix array.

Suffix Arrays. The suffix array of a string T is an array of integers that provides the starting position of T's suffixes, after they have been ordered lexicographically. Formally, if $T_{i,j}$ is the substring $t_it_{i+1} \ldots t_j$ of T and SA is the suffix array of T, then $T_{SA[1],n} < T_{SA[2],n} < \ldots < T_{SA[n],n}$. It is related to the BWT, since looking at the substrings preceding the terminating character $ in the BWM rows gives the suffixes of T in lexicographical order. In fact, the BWT can be derived in linear time from the suffix array by looping through its values and recording the character occurring just before each suffix in the original text, i.e. $BWT[i] = T[SA[i] - 1]$ if $SA[i] \neq 1$ and $BWT[i] = $ if $SA[i] = 1$. The suffix array coupled with the BWT and two additional data structures form the FM-index, which enables the backward search of a pattern in text.

Backward search Any occurrence of a pattern P in text is a prefix for some suffix of T, so all occurrences will be adjacent in the suffix array of T, since suffixes starting with P are sorted together in a SA-interval. The backward search starts with the last character of P and successively extends it to longer suffixes, calculating their SA-intervals, until the SA-interval of the entire query is reached. Let $C[a]$ be the total number of occurences in T of characters smaller than a in the alphabet, the C-array essentially representing the first column of the BWM. Then if P' is a suffix of the query P and $[l(P'), r(P')]$ is its corresponding SA-interval, then the search can be extended to aP' by calculating the new SA-interval:

$$l(aP') = C[a] + rank_{BWT}(a, l(P') - 1) + 1 \tag{1}$$

$$r(aP') = C[a] + rank_{BWT}(a, r(P)) \tag{2}$$

The search starts with the SA-interval of the empty string, $[1, n]$ and successively adds one character of P in backward order. When the search is completed,

it returns a SA-interval $[l, r]$ for the entire query P. If $r \geq l$, there are $r - l + 1$ matches for P and their locations in T are given by $SA[i]$ for $l \leq i \leq r$. Otherwise, the pattern does not exist in T. If the C-array and the ranks have already been stored, the backward search can be performed in $O(|P|)$ time in strings with DNA alphabet.

Wavelet Trees As the alphabet of a string contains more symbols, rank queries become more computationally expensive since they scale linearly with the alphabet size. The wavelet tree is a data structure designed to store strings with large alphabets efficiently and provide rank calculations in logarithmic time. A wavelet tree converts a string into a balanced binary-tree of bitvectors, whose root is built by taking the sorted alphabet and replacing the lower half of smaller symbols with a 0, and the other half of larger symbols with a 1 in the string. This creates ambiguity initially, but at each tree level, each half of the parent node's alphabet is re-split into 2 and re-encoded, so the ambiguity lessens as the tree is traversed in depth. At the leaves, there is no ambiguity at all. The tree is defined recursively as follows: take the lexicographically ordered alphabet, split it into 2 equal halves; in the string corresponding to the current node (start with original string at root), replace the first half of letters with 0 and the other half with 1; the left child node will contain the 0-encoded symbols and the right child node will contain the 1-encoded symbols, preserving their order from the original string; reapply the first step for each child node recursively until the alphabet left in each node contains only one or two symbols (so a 0 or 1 determines which symbol it is). An example is given in the figure below.
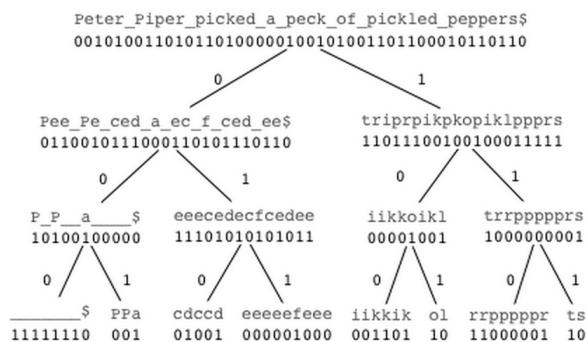

Fig. 1. Bla

In order to answer a rank query over the original string with large alphabet, repeated rank queries over the bitvectors in the wavelet tree nodes are used as a guide to the right subtree that contains the leaf where the queried symbol is non-ambiguously encoded. The rank of the queried symbol in this leaf is equal

to its rank in the original string. The number of rank queries needed to reach the leaf is equal to the height of the tree, i.e. $\log_2 |\Sigma|$ if we let Σ be the set of symbols in the alphabet. Computing ranks over binary vectors can be done in constant time, so a rank query in a wavelet tree-encoded string has complexity $O(\log_2 |\Sigma|)$. Next, we will show how the data structures described in this section can be used to store variation inside a reference genome in a way that supports read mapping.

2 Encoding a variation-aware reference structure

We propose a linear PRG conceptually equivalent with a directed, acyclic, partial order graph, that is generated from a reference sequence and a set of alternative sequences at given variation loci. The graph is linearised into a long string over an alphabet extended with new symbols marking the variants, for which the FM-index can be constructed. Building this data structure requires multiple steps.

1. First, homologous regions of shared sequence between the input reference genomes must be identified. These must be of size k at least (where k is pre-defined), and will act like anchors for the coordinates of the variation sites.
2. Second, for any locus between two anchor regions, the set of possible haplotypes must be determined from the input genomes, but they do not need to be aligned. Indels are naturally supported by haplotypes of different lengths.
3. Each variation locus is assigned two unique numeric identifiers, one even and one odd. The odd identifiers will mark locus boundaries and the even identifiers will mark alternative allele boundaries.
4. For each variation locus, its left anchor is added to the linear PRG, followed by its odd identifier. Then each sequence coming from that locus, starting with the reference sequence, is successively added to the linear PRG, followed by the even locus identifier, except the last sequence, which is followed by the odd identifier.
5. Convert the linear PRG to integer alphabet (A-¿1,C-¿2,G-¿3,T-¿4, variation locus identifiers-¿5,6,...)
6. The FM-index (suffix array, BWT, wavelet tree over BWT) of the linear PRG is constructed and we will call this the vBWT.

An illustration of these steps on a toy example is given in Figure.

Fig. 2. Bla

This vBWT construction allows reads to be mapped to it through a modified backward search algorithm. The variation markers that surround homologous alleles prevent wrong alignment across their boundaries and ensure the right path is taken when a read crosses a region with multiple alternative sequences. Since these markers are unique to each variation site, we can locate the beginning and end of a site in the Burrows-Wheeler matrix after the permutation of the linear PRG string. This enables reads to cross site junctions and map to the linear PRG when they span multiple sites of variation, allowing for new recombinations of known haplotypes. It also makes the method potentially adjustable for long reads. More importantly, the markers force the ends of alternative sequences coming from the same site to be sorted together in a separate block in the Burrows-Wheeler matrix, even if they do not have high sequence similarity. Therefore, homologous alleles from each site can be queried concurrently instead of looping through every one of them and checking if they match the read, which would happen if the markers were the same for all sites and non-homologous alleles got mixed up.

The linear PRG preserves information about the variant locations, so its coordinates can be projected back onto the primary reference sequence, enabling the integration with functional annotations and standard file formats. A path through the linear PRG is a string obtained by traversing the linear PRG and concatenating the non-variable segments with one sequence from each site that contains variation. If the first sequence is chosen from all variation sites, then the standard reference genome is obtained. Otherwise, a new alternative reference is obtained that can be used with usual software for downstream variant calling analysis. Our goal is to use the linear PRG mapping to genotype each of the variation sites, then use the link information from reads spanning multiple sites to phase adjacent variants and hence infer a personalised reference that corresponds to the path that is closest to the sample analysed.

3 Exact mapping

In this section, we present a modified backward search algorithm for exact matching against the vBWT that is aware of alternative sequence paths. When reads align to the non-variable part of of the linear PRG or when a variant locus is long enough to enclose the entire read, the usual backward search algorithm can be used. Otherwise, when the read must cross variation site junctions in order to align, site identifiers and some alternative alleles must be ignored by the search. This means a read can align to multiple substrings of the linear PRG that may not be adjacent in the BWM, so the search can return multiple SA-intervals. This is illustrated in figure.

At each step in backward search, before extending to the next character, we need to check whether the current matched read substring is preceded by a variation marker anywhere in the linear PRG. A scan for symbols larger than 4 must be performed in the BWT within the range given by the current SA-interval (need to explain range search 2d in a wavelet tree). If a variation marker is found

and it is an odd number, the read is about cross a site boundary, i.e. is about to walk in or walk out of a site. The suffix array can be queried to find the position of the two odd numbers in the liner PRG: the number occurring at a smaller position will mark the beginning of site and the other one will mark the end of site. If the search cursor is next to the start of the site, it is just the site marker that needs to be skipped so the SA-interval (size 1) of the suffix starting with that marker needs to be added to the set of intervals that will be extended with the next character in the read. If the search cursor is next to the end of a site, all alternative alleles from that site need to be queried. Their ends are sorted together in the BWM because of the markers, so they can be queried concurrently by adding the SA-interval of suffixes starting with all numbers marking that site (even and odd).

If the variation marker found is an even number, the read is about to cross an allele boundary, which means its current suffix matches the beginning of an alternative allele and the read is about to walk out of a site, so the search cursor needs to jump to the start of site. As previously described, the odd markers corresponding to that site can be found in the sorted first column of the BWM, and then querying the suffix array decides which one marks the start of site. Then the SA-interval (size 1) for the BWM row starting with this odd marker is recorded.

Once the check for variation markers is finished and all candidate SA-intervals have been added, each interval can be extended with the next character in the read by using equations 1 and 2.

Headings. Headings should be capitalized (i.e., nouns, verbs, and all other words except articles, prepositions, and conjunctions should be set with an initial capital) and should, with the exception of the title, be aligned to the left. Words joined by a hyphen are subject to a special rule. If the first word can stand alone, the second word should be capitalized.

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Lemmas, Propositions, and Theorems. The numbers accorded to lemmas, propositions, and theorems, etc. should appear in consecutive order, starting with Lemma 1, and not, for example, with Lemma 11.

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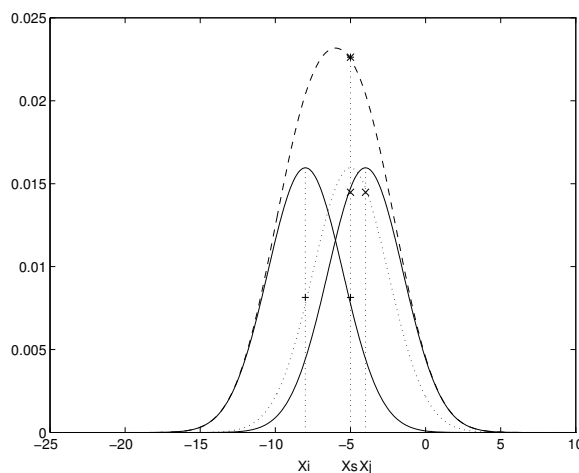

Fig. 3. One kernel at x_s (*dotted kernel*) or two kernels at x_i and x_j (*left and right*) lead to the same summed estimate at x_s. This shows a figure consisting of different types of lines. Elements of the figure described in the caption should be set in italics, in parentheses, as shown in this sample caption.

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$$\psi(u) = \int_o^T \left[\frac{1}{2} \left(\Lambda_o^{-1} u, u \right) + N^*(-u) \right] dt \ . \tag{3}$$

Equations should be punctuated in the same way as ordinary text but with a small space before the end punctuation mark.

3.3 Footnotes

The superscript numeral used to refer to a footnote appears in the text either directly after the word to be discussed or – in relation to a phrase or a sentence – following the punctuation sign (comma, semicolon, or period). Footnotes should appear at the bottom of the normal text area, with a line of about 2 cm set immediately above them.[1]

3.4 Program Code

Program listings or program commands in the text are normally set in typewriter font, e.g., CMTT10 or Courier.

Example of a Computer Program

```
program Inflation (Output)
  {Assuming annual inflation rates of 7%, 8%, and 10%,...
   years};
   const
     MaxYears = 10;
   var
     Year: 0..MaxYears;
     Factor1, Factor2, Factor3: Real;
   begin
     Year := 0;
     Factor1 := 1.0; Factor2 := 1.0; Factor3 := 1.0;
```

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[1] The footnote numeral is set flush left and the text follows with the usual word spacing.

```
    WriteLn('Year   7% 8% 10%'); WriteLn;
    repeat
      Year := Year + 1;
      Factor1 := Factor1 * 1.07;
      Factor2 := Factor2 * 1.08;
      Factor3 := Factor3 * 1.10;
      WriteLn(Year:5,Factor1:7:3,Factor2:7:3,Factor3:7:3)
    until Year = MaxYears
end.
```

(Example from Jensen K., Wirth N. (1991) Pascal user manual and report. Springer, New York)

3.5 Citations

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References

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4. Czajkowski, K., Fitzgerald, S., Foster, I., Kesselman, C.: Grid Information Services for Distributed Resource Sharing. In: 10th IEEE International Symposium on High Performance Distributed Computing, pp. 181–184. IEEE Press, New York (2001)
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6. National Center for Biotechnology Information, `http://www.ncbi.nlm.nih.gov`

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