Abstract. In this paper we present an efficient external memory algorithm to compute the string graph from a collection of reads, which is a fundamental data representation used for sequence assembly.

Our algorithm builds upon some recent results on lightweight Burrows-Wheeler Transform (BWT) and Longest Common Prefix (LCP) construction providing, as a by-product, an efficient procedure to extend intervals of the BWT that could be of independent interest.

We have implemented our algorithm and compared its efficiency against SGA—the most advanced assembly string graph construction program.

1 Introduction

De novo sequence assembly is a fundamental step in analyzing data from Next-Generation Sequencing (NGS) technologies. NGS technologies produce, from a given (genomic or transcriptomic) sequence, a huge amount of short sequences, called reads—the most widely used current technology can produce $10^9$ reads with average length 150. The large majority of the available assemblers [15,10,1] are built upon the notion of de Bruijn graphs where each $k$-mer is a vertex and an arc connects two $k$-mers that have a $k-1$ overlap in some input read. Also in transcriptomics, assembling reads is a crucial task, especially when analyzing RNA-seq in absence of a reference genome.

Alternative approaches to assemblers based on de Bruijn graphs have been developed recently, mostly based on the idea of string graph, initially proposed by Myers [9] before the advent of NGS technologies and further developed [13,14] to incorporate some advances in text indexing, such as the FM-index [7]. This method builds an overlap graph whose vertices are the reads and where an arc connects two reads with a sufficiently large overlap. For the purpose of assembling a genome some arcs might be uninformative. In fact an arc $(r_1, r_2)$ is called reducible if its removal does not change the strings that we can assemble from the graph, therefore reducible arcs can be discarded. The final graph, where all reducible arcs are removed, is called the string graph. More precisely, an arc $(r_1, r_2)$ of the overlap graph is labeled by a suffix of $r_2$ so that traversing a path $r_1, \ldots, r_k$ and concatenating the first read $r_1$ with the labels of the arcs of the path gives the assembly of the reads along the path [9].

The naïve way of computing all overlaps consists of pairwise comparisons of all input reads, which is quadratic in the number of reads. A main contribution of [13] is the use of the notion of $Q$-interval to avoid such pairwise comparisons. More precisely,
for each read \( r \) in the collection \( R \), the portion of BWT (Q-interval), identifying all reads whose overlap with \( r \) is a string \( Q \), is computed in time linear in the length of \( r \). In a second step, Q-intervals are extended to discover irreducible arcs. Both steps require to keep the whole FM-index and BWT for \( R \) and for the collection of reversed reads in main memory since the Q-intervals considered cover different positions of the whole BWT. Notice that the algorithm of [13] requires to recompute Q-intervals a number of times that is equal to the number of different reads in \( R \) whose suffix is \( Q \), therefore that approach cannot be immediately translated into an external memory algorithm. For this reason, an open problem of [13] is to reduce the space requirements by developing an external memory algorithm to compute the string graph.

Recently, an investigation of external memory construction of the Burrows-Wheeler Transform (BWT) and of related text indices (such as the FM-index) and data structures (such as LCP) has sprung [2,6,3] greatly reducing the amount of RAM necessary. In this paper, we show that two scans of the BWT, LCP and the generalized suffix array (GSA) for the collection of reads are sufficient to build a compact representation of the overlap graph, mainly consisting of the Q-intervals for each overlap \( Q \).

Since each arc label is a prefix of some reads and a Q-interval can be used to represent any substring of a read, we exploit the above representation of arcs also for encoding labels. The construction of Q-intervals corresponding to labels is done by iterating the operation of backward \( \sigma \)-extension of a Q-interval, that is computing the \( \sigma Q \)-interval on the BWT starting from a Q-interval. The idea of backward extension is loosely inspired by the pattern matching algorithm using the FM-index [7]. A secondary memory implementation of the operation of backward extension is a fundamental contribution of [2]. They give an algorithm that, with a single scan of the BWT, reads a lexicographically sorted set of disjoint Q-intervals and computes all possible \( \sigma Q \)-intervals, for every symbol \( \sigma \) (the original algorithm extends all Q-intervals where all Qs have the same length, but it is immediate to generalize that algorithm to an input set of disjoint Q-intervals). Our approach requires to backward extend generic sets of Q-intervals. For this purpose, we develop a procedure (ExtendIntervals) that will be a crucial component of our algorithm to build the overlap and string graph.

Our main result is an efficient external memory algorithm to compute the string graph of a collection of reads. The algorithm consists of three different phases, where the second phase consists of some iterations. Each part will be described as linear scans and/or writes of the files containing the BWT, the GSA and the LCP array, as well as some other intermediate files. We strive to minimize the number of passes over those files, as a simpler adaptation of the algorithm of [13] would require a number of passes equal to the number of input reads in the worst case, which would clearly be inefficient.

After building the overlap graph, where each arc consists of two reads with a sufficiently large overlap, the second phase iteratively extends the Q-intervals found in the first phase, and the results of the previous iterations to compute an additional symbol of some arc labels (all labels are empty at the end of the first phase). At the end of the second phase, those labels allow to reconstruct the entire assembly (i.e. the genome/transcriptome from which the reads have been extracted). Finally, the third phase is devoted to testing whether an arc is reducible, in order to obtain the final
string graph, using a new characterization of reducible arcs in terms of arc labels, i.e. prefixes of reads.

The algorithm has $O(dl^2 n)$ time complexity, where $l$ and $n$ are the length and the number of input reads and $d$ is the indegree of the string graph. We have developed an open source implementation of the algorithm, called LightStringGraph (LSG), available at http://lsg.algolab.eu/. We have compared LSG with SGA [13] on a dataset of 37M reads, showing that LSG is competitive (its running time is 5h 28min while SGA needed 2h 19min) even if disk accesses are much slower than those in main memory (SGA is an in-memory algorithm).

2 Preliminaries

We briefly recall the standard definitions of Generalized Suffix Array and Burrows-Wheeler Transform on a set of strings. Let $\Sigma$ be an ordered finite alphabet and let $S$ a string over $\Sigma$. We denote by $S[i]$ the $i$-th symbol of $S$, by $l = |S|$ the length of $S$, and by $S[i : j]$ the substring $S[i]S[i + 1] \cdots S[j]$ of $S$. The reverse of $S$ is the string $S^{rev} = S[l]S[l - 1] \cdots S[1]$. The suffix and prefix of $S$ of length $k$ are the substrings $S[l - k + 1 : l]$ and $S[1 : k]$, respectively. The $k$-suffix of $S$ is the suffix of length $k$.

Given two strings ($S_i$, $S_j$), we say that $S_i$ overlaps $S_j$ iff a nonempty suffix $Z$ of $S_i$ is also a prefix of $S_j$, that is $S_i = XZ$ and $S_j = ZY$. In that case we say that $S_j$ extends $S_i$ by $|Y|$ symbols, that $Z$ is the overlap of $S_i$ and $S_j$, denoted as $ov_{i,j}$, that $Y$ is the extension of $S_i$ with $S_j$, denoted as $ex_{i,j}$, and $X$ is the prefix-extension of $S_i$ with $S_j$, denoted as $pe_{i,j}$.

In the following of the paper we will consider a collection $R = \{r_1, \ldots, r_n\}$ of $n$ reads (i.e., strings) over $\Sigma$. As usual, we append a sentinel symbol $\$ \notin \Sigma$ to the end of each string ($\$$ lexicographically precedes all symbols in $\Sigma$). Then, let $R = \{r_1\$, \ldots, $r_n\$\}$ be a collection of $n$ strings (or reads), where each $r_i$ is a string over $\Sigma$; we denote by $\Sigma^\$ the extended alphabet $\Sigma \cup \{\$\}$. Moreover, we assume that the sentinel symbol $\$ is not taken into account when computing overlaps between two strings.

The Generalized Suffix Array (GSA) [12] of $R$ is the array $SA$ where each element $SA[i]$ is equal to $(k, j)$ if and only if the $k$-suffix of string $r_j$ is the $i$-th smallest element in the lexicographic order of the set of all the suffixes of the strings in $R$. We can build the GSA so that, whenever two reads $r_i$ and $r_j$ share a common $k$-suffix, then $(k, i)$ precedes $(k, j)$ in the GSA if and only if $r_i$ is lexicographically smaller than $r_j$. This fact implies that the first $|R|$ elements of the GSA correspond to $R$ in lexicographical order. To achieve that property, we need two scans of the GSA. The first scan extracts the sequence of pairs $(k, j)$ where $k$ is equal to the length of $r_j$, hence obtaining the reads of $R$ sorted lexicographically. The second scan uses the sorted $R$ to reorder consecutive entries of the GSA sharing the same suffix. This ordering will be exploited in the definition of a particular operation (the backward $\$$-extension). The Longest Common Prefix of $R$, denoted by $LCP$, is an array of size equal to the total length of the strings in $R$ and such that $LCP[i]$ is equal to the length of the longest prefix shared by the suffixes pointed to by $GSA[i]$ and $GSA[i - 1]$ (excluding the sentinel $\$$). For convenience, we assume that $LCP[1] = 0$. Notice that no element of $LCP$ is larger than the maximum length of a read of $R$. 
The Burrows-Wheeler Transform (BWT) of $R$ is the sequence $B$ such that $B[i] = r_j[|r_j| - i + 1]$ if $SA[i] = (j, k)$ and $k < |r_j|$, or $B[i] = \$\$, otherwise. Informally, $B[i]$ is the symbol that precedes the $k$-suffix of string $r_j$ where such suffix is the $i$-th smallest suffix in the ordering given by $SA$. Given a string $Q$, all suffixes of the GSA whose prefix is $Q$ appear consecutively in GSA, therefore they induce an interval $[b, e]$ which is called $Q$-interval [2] and denoted by $q(Q)$. We define the length and width of the $Q$-interval $[b, e]$ as $|Q|$ and the difference $(e - b)$, respectively. Notice that the width of the $Q$-interval is equal to the number of occurrences of $Q$ as a substring of some string $r \in R$. Whenever the string $Q$ is not specified, we will use the term string-interval to point out that it is the interval on the GSA of all suffixes having a common prefix. Since the BWT and the GSA are closely related, we also say that $[b, e]$ is a string-interval (or $Q$-interval for some string $Q$) on the BWT. Let $B^{rev}$ be the BWT of the set $R^{rev} = \{ r^{rev} \mid r \in R \}$, let $[b, e]$ be the $Q$-interval on $B$ for some string $Q$, and let $[b', e']$ be the $Q^{rev}$-interval on $B^{rev}$. Then, $[b, e]$ and $[b', e']$ are called linked. The linking relation is a 1-to-1 correspondence and two linked intervals have same width and length, hence $(e - b) = (e' - b')$.

Given a $Q$-interval and a symbol $\sigma \in \Sigma$, the backward $\sigma$-extension of the $Q$-interval is the $\sigma Q$-interval (that is, the interval on the GSA of the suffixes sharing the common prefix $\sigma Q$). We say that a $Q$-interval has a nonempty (empty, respectively) backward $\sigma$-extension if the resulting interval has width greater than 0 (equal to 0, respectively). Conversely, the forward $\sigma$-extension of a $Q$-interval is the $Q\sigma$-interval. Given the BWT $B$, the FM-index [7] is essentially composed of two functions $C$ and $Occ: C(\sigma)$, with $\sigma \in \Sigma$, is the number of occurrences in $B$ of symbols that are alphabetically smaller than $\sigma$, while $Occ(\sigma, i)$ is the number of occurrences of $\sigma$ in the prefix $B[i : i - 1]$ (hence $Occ(\$, 1) = 0). These two functions can be used to efficiently compute a backward $\sigma$-extension on $B$ of any $Q$-interval [7] and the corresponding forward $\sigma$-extension of the linked $Q^{rev}$-interval on $B^{rev}$ [8]. The same procedure can be used also for computing backward $\sigma$-extensions only thanks to the property that the first $|R|$ elements of the GSA corresponds to $R$ in lexicographical order.

3 The algorithm

Since short overlaps are likely to appear by chance, they are not meaningful for assembling the original sequence. Hence, we will consider only overlaps at least $\tau$ long, where $\tau$ is a positive constant. For simplicity, we assume that the set $R$ of the reads is substring-free, that is, there are no two reads $r_1, r_2 \in R$ such that $r_1$ is a substring of $r_2$. The overlap graph of $R$ is the directed graph $G_O = (R, A)$ whose vertices are the strings in $R$, and two reads $r_i, r_j$ form the arc $(r_i, r_j)$ if they overlap. Moreover, each arc $(r_i, r_j)$ of $G_O$ is labeled by the extension $ex_{i,j}$ of $r_i$ with $r_j$. Each path $(r_1, \cdots, r_k)$ in $G_O$ represents a string that is obtained by assembling the reads of the path. More precisely, such string is the concatenation $r_1 ex_{1,2} ex_{2,3} \cdots ex_{k-1,k}$ [14]. An arc $(r_i, r_j)$ of $G_O$ is called reducible if there exists another path from $r_i$ to $r_j$ representing the same string of the path $(r_i, r_j)$ (i.e., the string $r_i ex_{i,j}$). Notice that reducible arcs are not helpful in assembling reads, therefore we are interested in removing (or in avoiding computing) them. The resulting graph is called string graph [9].
Let us denote by $R^s(Q)$ and $R^p(Q)$ the set of reads whose suffix (prefix, resp.) is a given string $Q$. If $|Q| \geq \tau$, then each pair of reads $r_s \in R^s(Q)$, $r_p \in R^p(Q)$ forms an arc $(r_s, r_p)$ of $G_O$. Conversely, given an arc $(r_s, r_p)$ of $G_O$, then $r_s \in R^s(ov_{s,p})$ and $r_p \in R^p(ov_{s,p})$. Therefore, the arc set of the overlap graph is the union of $R^s(Q) \times R^p(Q)$ for each $Q$ at least $\tau$ characters long. Observe that a $QS$-interval represents the set $R^p(Q)$ of the reads with prefix $Q$, while a $QS$-interval represents the set $R^s(Q)$ of the reads with suffix $Q$. As a consequence, we can represent the sets $R^s(Q)$ and $R^p(Q)$ as two string-intervals.

Our algorithm for building the string graph is composed of three steps. The first step computes a compact representation of the overlap graph in secondary memory, the second step computes the prefix-extensions of each arc of the overlap graph that will be used in the third step for removing the reducible arcs from the compact representation of the overlap graph (hence obtaining the string graph). In the first step, since the cartesian product $R^s(S) \times R^p(S)$ represents all arcs whose overlap is $S$, we compute the (unlabeled) arcs of the overlap graph by computing all $S$-intervals ($|S| \geq \tau$) such that the two sets $R^s(S)$, $R^p(S)$ are both nonempty. We compactly represent the set of arcs whose overlap is $S$ as a tuple $(q(S\$), q($S\$), 0, |S\$))$, that we call basic arc-interval. We will use $S$ for denoting a string that is an overlap among some reads.

The three steps of the algorithm work on the three files—$B$, $S\!A$ and $L$—containing the BWT, the GSA, and the LCP of the set $R$, respectively. We first discuss the ideas used to compute the overlap graph, while we will present the other steps in the following parts of the section. Observe that the arcs of the overlap graph correspond to nonempty $S\$-$S$-intervals and $S$-$S$-intervals for every overlap $S$ of length at least $\tau$. As a consequence, the computation of the overlap graph reduces to the task of computing the set of $S$-intervals that have a nonempty backward and forward $-$extension (along with the extensions themselves). We first show how to compute in secondary memory all such $S$-intervals and their nonempty $-$extensions with a single sequential scan of $L$ and $S\!A$. Then, we will describe the procedure $\text{ExtendIntervals}$ that computes, in secondary memory and with a single scan of files $B$ and $L$, the backward $\sigma$-extensions of a collection of string-intervals (in particular, those computed before). Such a collection is not necessarily composed of pairwise-disjoint string-intervals, hence the procedure of $[\mathbb{D}]$ cannot be applied. We point out that $\text{ExtendIntervals}$ is of more general interest and, in fact, it will be also used in the second step of the algorithm.

An $S$-interval $[b, e]$ corresponds to a maximal portion $LCP[b+1:e-1]$ of values greater than or equal to $|S|$, that we call $|S|$-superblock. Moreover, if $S$ is an overlap between at least two reads, the width of such superblock is greater than 1. Notice that for each position $i$ of the LCP and for each integer $j$, there exists at most one $j$-superblock containing $i$. During a single scan of the LCP, for each position $i$, we can maintain the list of $j$-superblocks for all possible $j$ (i.e., all the string-intervals for some string $S$ such that $|S| = j$) that contain $i$. Such a list of superblocks represents the list of possible string-intervals that need to be forward and backward $-$extended to compute $R^s(S)$ and $R^p(S)$. Since the GSA contains all suffixes in lexicographic order, the $S$-$S$-interval (if it exists) is the initial portion $[b, e_1]$ of the $S$-interval $[b, e]$ such that, for each $b \leq i < e_1$, we have $SA[i] = (|S|, \cdot)$. Thus, by a single scan of the LCP file and of the GSA file, we complete the computation of all the $S$-$S$-intervals. This first scan
can also maintain the corresponding \( S \)-intervals. Then, a backward \( S \)-extension of this collection of \( S \)-intervals determines if the \( SS \)-interval is nonempty. As noted before, the \( S \)-intervals might not be disjoint, therefore the procedure of [5] cannot be applied. However, we produce this collection of \( S \)-intervals ordered by their end boundary. We developed the procedure \texttt{ExtendIntervals} (illustrated below) that, given a list of string-intervals ordered by their end boundary on the BWT, with a single scan of the files \( B \) and \( L \), outputs the backward \( \sigma \)-extensions of all the string-intervals given in input. Moreover, if pairs of linked intervals (\( i.e. \), pairs composed of an \( S \)-interval on \( B \) and the linked \( S^\text{rev} \)-interval on \( B^\text{rev} \)) are provided as input of \texttt{ExtendIntervals}, then it simultaneously computes the backward extensions of the intervals on \( B \) and the forward extensions of the intervals on \( B^\text{rev} \). Consequently, if we give as input of \texttt{ExtendIntervals} the collection of all \( S \)-intervals that have a nonempty forward \( S \)-extension, then we will obtain the collection of \( SS \)-intervals, that, coupled with the \( SS \)-intervals computed before, provide the desired compact representation of the overlap graph. Finally, we remark that the same procedure \texttt{ExtendIntervals} will be also crucial for computing the prefix-extensions in the second step of our algorithm.

### Backward extending \( Q \)-intervals.

In this section, we will describe a procedure for computing the backward extensions of a generic set \( I \) of string-intervals. Differently from the procedure in [5], which is only able to backward extend sets of pairwise disjoint string-intervals, we exploit the LCP array in order to efficiently deal with the inclusion between string-intervals (in fact, any two string-intervals are either nested or disjoint). Each \( Q \)-interval \([b, e]\) in \( I \) is associated to a record \((Q, [b, e], [b', e'])\) such that \([b, e]\) is the \( Q \)-interval on \( B \) and \([b', e']\) is the \( Q^\text{rev} \)-interval on \( B^\text{rev} \), that is, the intervals in each record are linked. Moreover, a set \( x([b, e]) \) of symbols are associated to each string-interval \([b, e]\) in \( I \), and \( x([b, e]) \) contains the symbols that must be used to extend the record. For each string-interval and for each character \( \sigma \) in the associated set of symbols, the result must contain a record \((\sigma Q, [b_\sigma, e_\sigma], [b'_\sigma, e'_\sigma])\) where \([b_\sigma, e_\sigma]\) is the backward \( \sigma \)-extension of \([b, e]\) on \( B \) and \([b'_\sigma, e'_\sigma]\) is the forward \( \sigma \)-extension of \([b', e']\) on \( B^\text{rev} \). Notice that also the intervals in the output records are linked.

The algorithm \texttt{ExtendIntervals} performs only a single pass over the BWT \( B \) and the LCP \( L \), and maintains an array \( II[\cdot] \) which stores for each symbol in \( \Sigma^S \) the number of its occurrences in the prefix of the BWT preceding the current position. In other words, when the first \( p \) symbols of \( B \) have been read, the array \( II \) gives the number of occurrences of each symbol in \( \Sigma^S \) in the first \( p - 1 \) characters of \( B \). The procedure also maintains some arrays \( EII[\cdot] \) so that, for each symbol \( \sigma \) and each integer \( j \), \( EII[\sigma] = \text{Occ}(\sigma, p_j) \) where \( p_j \) is the starting position of the \( Q \)-interval containing the current position of the BWT such that (1) \(|Q| = j \) and (2) the width of the \( Q \)-interval is larger than 1. Notice that, for each position \( p \) and integer \( j \), at most one such \( Q \)-interval exists. If no such \( Q \)-interval exists then the value of \( EII_j \) is undefined. We recall that \( \text{Occ}(\sigma, p) \) is the number of occurrences of \( \sigma \) in \( B[0 : p - 1] \). Since \texttt{ExtendIntervals} accesses sequentially the arrays \( B \) and \( LCP \), it is immediate to view the procedure as an external memory algorithm where \( B \) and \( LCP \) are two files. Notice also that
Proof. We prove the lemma by induction on suffixes in the interval \( i \geq 1 \), therefore the initialization of line 1 sets the correct values of \( E \) and \( Q \) is updated only at line 16, hence its correctness is immediate.

Moreover all string-intervals containing the position 1 must start at 1 (as no position \( p \) position of width larger than \( c \) occurs in \( B \)).

Lemma 1. At line 3 of Algorithm 1, for each \( c \in \Sigma \) (1) \( \Pi[c] = \sum_{\sigma < c} (\Pi(\sigma) - E\Pi_{\Sigma}(\sigma)) + (1 - t) \) and (2) \( \Pi_{\Sigma}[c] = Occ(c, p_k) \) for each \( Q \)-interval \([p_k, e_k]\) of width larger than 1 which contains \( p \) and such that \(|Q| = k\).

Proof. We prove the lemma by induction on \( p \). When \( p = 1 \), there is no symbol before position \( p \), therefore \( \Pi \) must be made of zeroes, and the initialization of line 1 is correct. Moreover all string-intervals containing the position 1 must start at 1 (as no position precedes 1), therefore the initialization of line 1 sets the correct values of \( E\Pi_{\Sigma} \).

Assume now that the property holds up to step \( p - 1 \) and consider step \( p \). The array \( \Pi \) is updated only at line 16 hence its correctness is immediate.

Let \([p_k, e_k]\) be the generic \( Q \)-interval \([p_k, e_k]\) containing \( p \) and such that (1) \(|Q| = k\), and (2) the width of the \( Q \)-interval is larger than 1, that is \( e_k - p_k \geq 2 \). Since all suffixes in the interval \([p_k, e_k]\) of the GSA have \( Q \) as a common prefix and \(|Q| = k\), \( LCP[i] \geq k \) for \( p_k < i \leq e_k \).
If \( p_k < p \) then \([p_k, e_k)\) contains also \( p - 1 \), that is \( Q \) is a prefix of the suffix pointed to by \( SA[p - 1] \). Therefore \( LCP[p] \geq k \) and the value of \( EI_k \) at iteration \( p \) is the same as at iteration \( p - 1 \). By inductive hypothesis \( EI_k = Occ(c, p_k) \). The value of \( EI_k \) is correctly assigned in this case, since the line 14 of the algorithm is not executed.

Consider now the case \( p_k = p \), that is \( p \) is the beginning of the \( Q \)-interval, for some \( Q \) with \( |Q| = k \). In this case \( LCP[p] < k \). Therefore \( EI_k \) is updated at line 15 and, by the correctness of \( II \), is set to \( Occ(\cdot, p) \).

\[\text{Lemma 2.} \quad \text{Let} \ (Q, [b, e), [b', e')) \text{ be a record and let} \ c \in x([b, e)) \text{ be a character. Then Algorithm 1 outputs the correct c-extension of such record.}\]

\[\text{Proof.} \quad \text{When the algorithm reaches position} \ p = e, \ \text{it outputs a c-extension of the record} \ (Q, [b, e), [b', e')) \text{. Therefore we only have to show that the computed extension is correct.} \]

The backward c-extension of \([b, e)\) is \([C(c) + Occ(c, b) + 1, C(c) + Occ(c, e) + 1]\) \[8\], while the forward c-extension of its linked interval \([b', e')\) has starting point \( b' \) plus the number of occurrences in \( B[b:e-1] \) of the symbols smaller than \( c \) \[8\]. Moreover two linked intervals have the same width \[8\].

These observations, together with Lemma 1 and the fact that \( II \) and \( EII \) are not modified in lines 5, 6, 7, immediately establish the correctness for the case \( b < e - 1 \).

Let us now consider the case \( b = e - 1 \). Notice that \( Occ(c, p) = Occ(c, p - 1) \) unless \( B[p-1] = c \) and \( Occ(c, p) = Occ(c, p - 1) + 1 \) if \( B[p-1] = c \). Therefore the assignment of \( t \) at lines 7, 10 guarantees that, at line 11 \( Occ(c, p) = Occ(c, p - 1) + (1 - t) \). Combining that with Lemma 1, we obtain that \( II[c] + t = Occ(c, p) + t = Occ(c, p - 1) \), completing the proof.

\[\text{Computing arc labels.}\]

In this part, we describe how the compact representation of the overlap graph computed in the first step can be further processed in order to easily remove reducible arcs without resorting to (computationally expensive) string comparisons. First, we give an easy-to-test characterization of reducible arcs of overlap graphs in terms of string-intervals (Lemmas 3 and 4). Then, we show how such string-intervals (that we call \textit{arc-labels}) can be efficiently computed in external memory starting from the collection of basic arc-intervals computed in the first step.

\[\text{Lemma 3.} \quad \text{Let} \ G_O \text{ be the overlap graph for} \ R \text{ and let} \ (r_{i_1}, r_{i_2}, \ldots, r_{i_k}) \text{ be a path of} \ G_O. \text{Then, such a path represents the string} \ pe_{i_1, i_2}pe_{i_2, i_3} \cdots pe_{i_{k-1}, i_k}r_{i_k}.\]

\[\text{Proof.} \quad \text{We will prove the lemma by induction on} \ k. \text{ Let} \ (r_h, r_j) \text{ be an arc of} \ G_O. \text{ Notice that the string represented by such arc is} \ pe_{h, j}ov_{h, j}ex_{h, j}. \text{ Since} \ r_h = pe_{h, j}ov_{h, j} \text{ and} \ r_j = ov_{h, j}ex_{h, j} \text{, applying the property to the arc} \ (r_{i_1}, r_{i_j}) \text{ settles the case} \ k = 2. \]

Assume now that the lemma holds for paths of length smaller than \( k \) and consider the path \( (r_{i_1}, \ldots, r_{i_k}) \). By definition, the string represented by such path is \( r_{i_1}ex_{i_1, i_2} \cdots ex_{i_{k-1}, i_k} \). By inductive hypothesis on the path \( (r_{i_1}, r_{i_2}, \ldots, r_{i_{k-1}}) \), is equal to \( pe_{i_1, i_2} \cdots pe_{i_{k-2}, i_{k-1}}r_{i_{k-1}}ex_{i_{k-1}, i_k} \). But \( r_{i_{k-1}}ex_{i_{k-1}, i_k} = pe_{i_{k-1}, i_k}ov_{i_{k-1}, i_k}ex_{i_{k-1}, i_k} \).
which in turn can be rewritten as $pe_{i_{k-1},i_k}r_{i_k}$. Therefore $pe_{i_1,i_2} \cdots pe_{i_{k-2},i_{k-1}}r_{i_{k-1}} \tau x_{i_{k-1},i_k} = pe_{i_1,i_2} \cdots pe_{i_{k-2},i_{k-1}}pe_{i_k,i_{k+1}}r_{i_k}$ completing the proof. □

**Lemma 4.** Let $G_O$ be the overlap graph for a substring-free set $R$ of reads and let $(r_i,r_j)$ be an arc of $G_O$. Then, $(r_i,r_j)$ is reducible iff there exists another arc $(r_h,r_j)$ such that $pe_{h,j}$ is a proper suffix of $pe_{i,j}$ (or, equivalently, that $pe_{h,j}^{rev}$ is a proper prefix of $pe_{i,j}^{rev}$).

**Proof.** By definition, $(r_i,r_j)$ is reducible if and only if there exists a second path $(r_i,r_{h_1},\ldots,r_{h_k},r_j)$ representing the string $XYZ$, where $X$, $Y$ and $Z$ are respectively the prefix-extension, the overlap and the extension of $r_i$ with $r_j$ (notice that the sequence $(r_{h_1},\ldots,r_{h_k})$ might be empty).

Assume now that such a path $(r_i,r_{h_1},\ldots,r_{h_k},r_j)$ exists, therefore $r_{h_k}$ is a substring of $XYZ$. Since $r_{h_k}$ overlaps with $r_j$, $r_{h_k} = X_1YZ_1$ where $X_1$ is a suffix of $X$ and $Z_1$ is a proper prefix of $Z$. Notice that $X_1 = pe_{h,j}$. Moreover, $R$ is substring free, hence $X_1$ is a proper suffix of $X$, otherwise $r_i$ would be a substring of $r_{h_k}$, completing this direction of the proof.

Assume now that there exists an arc $(r_h,r_j)$ such that $pe_{h,j}$ is a proper suffix of $pe_{i,j}$. Again, $r_h = X_1Y_1Z_1$ where $X_1$, $Y_1$ and $Z_1$ are respectively the prefix-extension, the overlap and the extension of $r_{h_k}$ with $r_j$. By hypothesis, $X_1$ is a suffix of $X$. Since $r_h$ is not a substring of $r_i$, the fact that $X_1$ is a suffix of $X$ implies that $Y$ is a substring of $Y_1$, therefore $r_i$ and $r_h$ overlap and $|ov_{i,h}| \geq |Y| \geq \tau$, hence $(r_i,r_h)$ is an arc of $G_O$.

The string associated to the path $r_i,r_h,r_j$ is $r_iex_{i,h}ex_{h,j}$. By Lemma 3, $r_iex_{i,h}ex_{h,j} = pe_{i,h}pe_{h,j}r_j$. At the same time the string associated to the path $r_i,r_j$ is $r_iex_{i,j} = pe_{i,j}r_j$ by Lemma 3 hence it suffices to prove that $pe_{i,h}pe_{h,j} = pe_{i,j}$. Since $pe_{h,j}$ is a proper suffix of $pe_{i,j}$, by definition of prefix-extension, $pe_{i,h}pe_{h,j} = pe_{i,j}$, completing the proof. □

A corollary of Lemma 4 is that an arc $(r_i,r_j)$ is reducible iff there exists another arc $(r_h,r_j)$ such that the $pe_{h,j}^{rev}$-interval strictly contains the $pe_{i,j}^{rev}$-interval. As a consequence, it would be useful to compute and store the prefix-extensions of the arcs, obtaining a partition of each set $R^*(S) \times R^*(S)$ (i.e., of each basic arc-interval) in classes with the same prefix-extension $P$. More precisely, for each of those classes, we need the $PS$-interval as well as the $P$-interval to represent all arcs $(r_i,r_j)$ with $ov_{i,j} = S$ and label $pe_{i,j} = P$. However, in order to perform the reducibility test, the $pe_{i,j}$-interval alone is not sufficient, and we also need the $pe_{i,j}^{rev}$-interval. All these concepts are fundamental for describing our algorithm and are formally defined as follows.

**Definition 5.** Let $B$ be a BWT for a collection of reads $R$ and let $R^{rev}$ be the BWT for the reversed reads $R^{rev}$. Let $S$ and $P$ be two strings. Then, the arc-interval associated to $(P,S)$ is the tuple $(q(P$-$S$), $q(S$-$S$), $|P|$, $|PS$-$S$|), where $q(P$-$S$) and $q(S$-$S$) are the $PS$-interval and the $S$-$S$-interval on $B$. Moreover, $|PS$-$S|$, $S$ and $P$ are respectively called the length, the overlap-string, and the prefix-extension of the arc-interval.

An arc-interval is terminal if the $PS$-$S$-interval has a nonempty backward $S$-extension. The triple $(q(P), q^{rev}(P^{rev}), |P|)$ is called the arc-label of the arc-interval associated to $(P,S)$. 


To obtain the labels of the arcs we need to compute the terminal arc-intervals, that is the arc-intervals where \( P \) is the (complete) prefix-extension of an arc, since \( q(PS\$) \) (in a terminal arc-interval) has a nonempty backward \$\)-extension. If \( R \) is a substring-free set of strings, \( q(PS\$) \) represents a unique read \( r = PS \). The associated arc-labels are used to test efficiently whether an arc is reducible.

Terminal arc-intervals are computed by extending string-intervals \( q(PS\$) \) of arc-intervals by increasing length \(|PS|\). This step is done by modifying the approach in \cite{5} to deal, at each iteration of backward extension, with string-intervals that can be disjoint or duplicated (see procedure \texttt{ExtendArcIntervals}, Alg. \cite{2}). In fact, we may have two arc-intervals, associated to the pairs \((P_1, S_1)\) and \((P_2, S_2)\), which correspond to the same string-interval \( q(P_1S_1\$) = q(P_2S_2\$) \), where \( P_1S_1 = P_2S_2 \) but \( S_1 \neq S_2 \). Such duplicated arc-intervals will occur consecutively in the input list.

Arc-labels are computed by incrementally backward extending with \texttt{ExtendIntervals} the linked intervals \( q(P) \) and \( q^{rev}(P^{rev}) \) at the same iteration where interval \( q(PS\$) \) of the associated arc-interval has been extend. In fact, we maintain a link between an arc-interval and its arc-label. While at each iteration all string-intervals originating from arc-intervals have the same length, the string-intervals associated to arc-labels can have different lengths. However, in each file they are ordered by their end boundary, hence we can apply directly the \texttt{ExtendIntervals} procedure. By maintaining a suitable organization of the files, we are able to keep a 1-1 correspondence between arc-intervals and arc-labels.

When we compute an extension, we test if the arc-interval \((q(PS\$), q(S\$), |P|, |PS\$|)\) is terminal, that is if \( q(PS\$) \) has a nonempty backward \$\)-extension. In that case we have found the set \( \{r\} \times R^\circ(S) \) of arcs of the overlap graph outgoing from the read \( r = PS \) and with overlap \( S \).

Managing \( Q \)-intervals using files.

During the first step, the algorithm computes a file \( \texttt{BAIL}(\sigma, l_1) \), for each symbol \( \sigma \in \Sigma \) and for each integer \( l_1 \), such that \( \tau + 1 \leq l_1 \leq l_{\text{max}} \), where \( l_{\text{max}} \) is the maximum length of a read in \( R \). More precisely, the file \( \texttt{BAIL}(\sigma, l_1) \) contains the basic arc-intervals of length \( l_1 \), whose overlap-string begins with the symbol \( \sigma \) (observe that the overlap-string has length \( l_1 - 1 \)). The basic arc-intervals are stored (in each file) by non-decreasing values of the start boundary \( e \) of the interval \( q(S\$) = [b, e] \).

The algorithm also uses a file \( \texttt{AIL}(\sigma, l_1) \) and a file \( \texttt{ACL}(\sigma, l_1, l_2) \) for each symbol \( \sigma \in \Sigma \), for each integer \( l_1 \), such that \( \tau + 1 < l_1 \leq l_{\text{max}} \), and for each integer \( l_2 \) such that \( 1 \leq l_2 \leq l_{\text{max}} - \tau \). The file \( \texttt{AIL}(\sigma, l_1) \) consists of the arc-intervals of length \( l_1 \), whose prefix-extension \( P \) begins with the symbol \( \sigma \), while the file \( \texttt{ACL}(\sigma, l_1, l_2) \) contains the arc-labels related to arc-intervals of length \( l_1 \) whose \( l_2 \)-long prefix-extension \( P \) begins with the symbol \( \sigma \). These files are tightly coupled, since there is a 1-to-1 correspondence between records of \( \texttt{AIL}(\sigma, l_1) \) and records of \( \texttt{ACL}(\sigma, l_1, \cdot) \), where those records refer to the same pair \((P, S)\) of prefix-extension (of length \( l_2 \)) and overlap-string. Each of the \( \texttt{BAIL}(\cdot, \cdot), \texttt{AIL}(\cdot, \cdot) \) and \( \texttt{ACL}(\cdot, \cdot, \cdot) \) files contains string-intervals of the same length and ordered by start boundary, hence those intervals are also sorted by end boundary.
Algorithm 2: ExtendArcIntervals

Input : Two files $B$ and $SA$ containing the BWT and the GSA of the set $R$, respectively. A set of files $AI(\cdot, l_1)$ containing the arc-intervals of length $l_1$. A set of files $BAI(\cdot, l_1)$ containing the basic arc-intervals of length $l_1$. 

Output : A set of files $AI(\cdot, l_1 + 1)$ containing the arc-intervals of length $l_1 + 1$. The arcs of the overlap graph coming out from reads of length $l_1 - 1$.

1 $\Pi(\sigma) \leftarrow 0$, for each $\sigma \in \Sigma$; 
2 $\pi(\sigma) \leftarrow 0$, for each $\sigma \in \Sigma$; 
3 $[b_{prev}, e_{prev}] \leftarrow null$; 

foreach $\sigma \in \Sigma$ do 

5 foreach $([b, e], q(S), l_e, l_1) \in SortedMerge(AI(\cdot, l_1), BAI(\cdot, l_1))$ do 

// If the $PS$-interval $[b, e]$ is different from the one previously processed, then 

vectors $\Pi$ and $\pi$ must be updated, otherwise $[b, e]$ is extended using the values 

previously computed. 

6 if $([b, e] \neq [b_{prev}, e_{prev}]$ then 

7 $\Pi(\sigma) \leftarrow \Pi[\sigma] + \pi[\sigma]$, for each $\sigma \in \Sigma$; 
8 Update $\Pi$ while reading $B$ until the BWT position $b - 1$; 
9 $\pi(\sigma) \leftarrow 0$, for each $\sigma \in \Sigma$; 
10 $r \leftarrow null$; 

11 while reading $B$ from the BWT position $b$ to $e - 1$ do 

12 $\sigma \leftarrow$ symbol of the BWT at the current position $p$; 
13 if $\sigma \neq $ then 

14 $\pi[\sigma] \leftarrow \pi[\sigma] + 1$; 
15 else 

16 // The arc-interval is terminal and $r$ is the read equal to $PS$ 

17 $r \leftarrow$ the read pointed to by GSA at position $p$; 
18 if $r \neq null$ then 

19 // Update the file $A$ of the output arcs, since the arc-interval is terminal 

20 Append $\{r\} \times R^p(S)$ to $A|_{l_e}$; 
else 

21 foreach $\sigma \in \Sigma$ do 

22 if $\pi[\sigma] > 0$ then 

23 $b' \leftarrow C[\sigma] + \Pi[\sigma] + 1$; 
24 $e' \leftarrow b' + \pi[\sigma]$; 
25 Append $([b', e'], q(S), l_e + 1, l_1 + 1)$ to $A|_{l_1 + 1}$; 
26 $[b_{prev}, e_{prev}] \leftarrow [b, e]$;

Computing terminal arc-intervals and arc-labels.

After the first step, the algorithm computes terminal arc-intervals and arc-labels. The first fundamental observation is that an arc-interval of length \( l_1 + 1 \) (that is an arc-interval that will be stored in \( \text{BAT}(\cdot, l_1 + 1) \)), and corresponding to a pair \((P, S)\) with \(|PS| = l_1 + 1\), can be obtained by extending a basic arc-interval of length \( l_1 \) (taken from \( \text{BAT}(\cdot, l_1) \)) or a non-basic arc-interval of length \( l_1 \) (taken from \( \text{AI}(\cdot, l_1) \)). Since all those files are sorted, we can assume to have a SortedMerge procedure which receives two sorted files and returns their sorted union. Notice that we do not actually need to write a new file, as SortedMerge basically consists in choosing the file from which to read the next record.

The algorithm performs some extension steps, each mainly backward \( \sigma \)-extending string-intervals. In fact, at each extension step \( i \) (to simplify some formulae, the first step is set to \( i = \tau + 1 \)), the algorithm scans all files \( \text{BAT}(\cdot, i) \), \( \text{AI}(\cdot, i) \), \( \text{AL}(\cdot, i, j) \) and computes the files \( \text{AI}(\cdot, i + 1) \), \( \text{AL}(\cdot, i + 1) \). At iteration \( i \), for each \( \sigma_1 \in \Sigma \), all records in \( \text{SortedMerge}(\text{BAT}(\cdot, i, \sigma_1), \text{AI}(\cdot, i, \sigma_1)) \) are \( \sigma_2 \)-extended, for each \( \sigma_2 \in \Sigma \), via the procedure \text{ExtendArcIntervals}, outputting the results in the file \( \text{AI}(\cdot, i + 1) \). We recall that \( \sigma \)-extending a record means, in this case of the procedure \text{ExtendArcIntervals}, to backward \( \sigma \)-extend the \( q(PS) \) of the arc-interval (or the \( q(S) \) of the basic arc-interval). If the record to \( \sigma_2 \)-extend is read from a file \( \text{BAT}(\cdot, i) \) (i.e., it is a basic arc-interval), when the algorithm writes a record of \( \text{AI}(\cdot, i + 1) \) (i.e., the \( \sigma_2 \)-extension of those record), it also writes the corresponding record of \( \text{AL}(\cdot, i + 1) \), that is an arc-label where the prefix-extension is equal to the symbol \( \sigma_2 \). On the other hand, if the current record to \( \sigma_2 \)-extend is read from a file \( \text{AI}(\cdot, i) \), we consider also the corresponding record of \( \text{AL}(\cdot, i) \) to write a record of \( \text{AI}(\cdot, i + 1) \) and the corresponding record of \( \text{AL}(\cdot, i + 1) \) which is the \( \sigma_2 \)-extension of the record in \( \text{AL}(\cdot, i) \). Each time a terminal arc-interval associated to \((P, S)\) is found, the arcs \( \{r\} \times R^p(S) \), where \( r = PS \), are written in the file \( A_{\{P\}} \).

Testing irreducible arcs.

The algorithm reads the arcs of the overlap graph, stored in the files \( A_i \), for increasing values of \( i \). Each arc \( a \) is added to the set \( A \) of the arcs of the string graph if there is no arc already in \( A \) reducing \( a \). Notice that \( A \) is stored in main memory in the current implementation. Lemma 3 implies that an arc (of the overlap graph) associated to a pair \((P_1, S_1)\) can be reduced only by an arc associated to a pair \((P_2, S_2)\), such that \(|P_1| > |P_2|\). Hence, an arc in \( A_i \) can be reduced by an arc in \( A_j \) only if \( j < i \). Since we examine the files \( A_i \) by increasing values of \( i \), either an arc \( a \) is reduced by an arc that is already in \( A \), or no subsequently read arc of the overlap graph can reduce \( a \). Notice also that, by the reducibility test of Lemma 3, an arc associated to a pair \((P_1, S_1)\) is reduced by an arc associated to \((P_2, S_2)\) if and only if \( P_2^\text{rev} \) is a proper prefix of \( P_1^\text{rev} \). Thus, the test is equivalent to determine whether the \( P_2^\text{rev} \)-interval on \( B^\text{rev} \) properly contains the \( P_1^\text{rev} \)-interval. The latter test can be easily performed by outputting in the files \( A_j \) a representation of the prefix-interval of each arc.
On the complexity.

Notice that Algorithm 1 scans once $B$ and $L$ and recall the total length of $B$ is $ln$. Since the input $Q$-intervals are nested or disjoint, there are at most $O(ln)$ distinct $Q$-intervals, that is, block at lines 6–10 and line 12 are executed $O(ln)$ times. A stack-based data structure allows to store the distinct $\mathcal{E}\Pi$ arrays while requiring $O(1)$ time for each iteration, hence the time complexity of Algorithm 1 is $O(ln)$. The second phase of our algorithm consists of $(l-\tau)$ iterations, each requiring a call to $\text{ExtendIntervals}$ and $\text{ExtendArcIntervals}$, therefore the overall time complexity to compute the overlap graph is $O(l^2n)$, which is also an upper bound on the number of arcs of the overlap graph. The time complexity of the third phase is $O(de)$, where $e$ and $d$ are respectively the number of arcs of the overlap graph and the maximum indegree of the resulting string graph, as each arc must be tested for reducibility against each adjacent vertex.

4 Experimental Analysis

We performed a preliminary experimental comparison of LSG with SGA, a state-of-the-art assembler based on string-graphs [13], on the dataset of the Human chromosome 14 used in the recent Genome Assembly Gold-standard Evaluation (GAGE) project [11]. We used a slightly modified version of BEETL 0.9.0 [2] to construct the BWT, the GSA, and the LCP of the reads needed by LSG. Since the current version of BEETL requires all input reads to have the same length, we harmonized the lengths of the reads ($\sim 36M$) of the GAGE dataset to 90bp: we discarded shorter reads ($\sim 6M$), whereas we split longer reads into overlapping substrings with a minimum overlap of 70bp. We further preprocessed and filtered the resulting $\sim 50M$ reads according to the workflow used for SGA in GAGE [11]: no reads were discarded by the preprocess step, while $\sim 13M$ reads were filtered out as duplicated. As a result, the final dataset was composed of $\sim 37M$ reads of length 90bp.

We generated the index of the dataset using $\text{sga-index}$ and $\text{beetl-bwt}$ and we gave them as input to SGA and LSG requiring a minimum overlap ($\tau$) of 65. We performed the experimental analysis on a workstation with 12GB of RAM and standard mechanical hard drives, as our tool is designed to cope with a limited amount of main memory. The workstation has a quad-core Intel Xeon W3530 2.80GHz CPU running Ubuntu Linux 12.04. To perform a fair comparison, we slightly modified SGA to disable the computation of overlaps on different strands (i.e., when one read is reversed and complemented w.r.t. the other).

For the comparison, we focused on running times and main memory allocation. During the evaluation of the tools we do not consider the index generation step because such part is outside the scope of this paper. Regarding the running times, SGA built the string graph in 2 hours and 19 minutes, whereas LSG built the string graph in a total time of 5 hours and 28 minutes (9min were required for computing the basic arc-intervals, 5h and 13min for arc labeling, 4min for graph reduction, and 2min for producing the final output). Regarding the main memory usage, SGA had a peak memory allocation of 3.2GB whereas LSG required less than 0.09GB for basic arc-
interval computation and for arc labeling, less than 0.25GB for graph reduction, and about 2.5GB for producing the output.

We point out that the memory allocation is due almost exclusively to writing the string graph in the ASQG format (the format used by SGA), as all the other steps required at most 250MB of main memory. We also want to point out that the memory required by the reduction step can be arbitrarily reduced by reducing iteratively arcs incident to subsets of nodes with only a small penalty in running times. We chose to write the output in ASQG format (despite it causes a significant increase in memory usage) to allow processing the results obtained by LSG by the subsequent steps of the SGA workflow (such as the assembly and the alignment steps).

Furthermore, we point out that this experimental part was performed on commodity hardware equipped with mechanical hard disks. As a consequence, the execution of LSG on systems equipped with faster disks (e.g., SSDs) will significantly decrease its running time, especially when compared with SGA.

5 Conclusions and future work

We have proposed an external memory algorithm for building a string graph from a set $R$ of reads and we have shown that our approach is efficient in theory (the time complexity is not much larger than that of the lightweight BWT construction, which is a necessary step) and in practice (the time required by LSG is less than 3 times that of SGA, while memory usage in all the most computationally expensive steps is less than 12 times that of SGA) on a regular PC.

Since LSG potentially scales on very large datasets, we expect to be able to use our approach to assemble RNA-seq reads even when the entire transcriptome is sequenced at high coverage. In fact, an important research direction is to face the problem of assembling RNA-seq data and building graph models of gene structures (such as splicing graphs [4]) in absence of a reference genome.

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