

# Fast Algorithms for Finding Maximum-Density Segments of a Sequence with Applications to Bioinformatics

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**Abstract.** We study an abstract optimization problem arising from biomolecular sequence analysis. For a sequence  $A = \langle a_1, a_2, \dots, a_n \rangle$  of real numbers, a *segment*  $S$  is a consecutive subsequence  $\langle a_i, a_{i+1}, \dots, a_j \rangle$ . The *width* of  $S$  is  $j - i + 1$ , while the *density* is  $(\sum_{i \leq k \leq j} a_k) / (j - i + 1)$ . The *maximum-density segment* problem takes  $A$  and two integers  $L$  and  $U$  as input and asks for a segment of  $A$  with the largest possible density among those of width at least  $L$  and at most  $U$ . If  $U = n$  (or equivalently,  $U = 2L - 1$ ), we can solve the problem in  $O(n)$  time, improving upon the  $O(n \log L)$ -time algorithm by Lin, Jiang and Chao for a general sequence  $A$ . Furthermore, if  $U$  and  $L$  are arbitrary, we solve the problem in  $O(n + n \log(U - L + 1))$  time. There has been no nontrivial result for this case previously. Both results also hold for a weighted variant of the maximum-density segment problem.

## 1 Introduction

Non-uniformity of nucleotide composition within genomic sequences was first revealed through thermal melting and gradient centrifugation experiments [19,22]. The GC content of the DNA sequences in all organisms varies from 25% to 75%. GC-ratios have the greatest variations among bacteria's DNA sequences, while the typical GC-ratios of mammalian genomes stay in 45-50%. The GC content of human DNA varies widely throughout the genome, ranging between 30% and 60%. Despite intensive research effort in the past two decades, the underlying causes of the observed heterogeneity remain contested [2,4,5,7,8,10,11,16,32,34]. Researchers [25,31] observed that the compositional heterogeneity is highly correlated to the GC content of the genomic sequences. Other investigations showed

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that gene length [6], gene density [36], patterns of codon usage [29], distribution of different classes of repetitive elements [6, 30], number of isochores [2], lengths of isochores [25], and recombination rate within chromosomes [12] are all correlated with GC content. More research related to GC-rich segments can be found in [13, 15, 18, 20, 23, 24, 27, 33, 35] and the references therein.

Although GC-rich segments of DNA sequences are important in gene recognition and comparative genomics, only a couple of algorithms for identifying GC-rich segments appeared in the literature. A widely used window-based approach is based upon the GC-content statistics of a fixed-length window [9, 14, 25, 26]. Due to the fixed length of windows, these practically fast approaches are likely to miss GC-rich segments that span more than one window. Huang [17] proposed an algorithm to accommodate windows with variable lengths. Specifically, by assigning  $-p$  points to each AT-pair and  $1 - p$  points to each GC-pair, where  $p$  is a number with  $0 \leq p \leq 1$ , Huang gave a linear-time algorithm for computing a segment of length no less than  $L$  whose score is maximized. As observed by Huang, however, this approach tends to output segments that are significantly longer than the given  $L$ .

In this paper, we study a previous abstraction of the problem. Let  $A = \langle a_1, a_2, \dots, a_n \rangle$  be a sequence of real numbers. A *segment*  $S$  of  $A$  is a consecutive subsequence  $\langle a_i, a_{i+1}, \dots, a_j \rangle$ . The *width* of  $S$  is  $j - i + 1$ , i.e., the number of entries in  $S$ . The *density* of  $S$  is simply the average  $(\sum_{i < k \leq j} a_k) / (j - i + 1)$ . Let  $L$  and  $U$  be positive integers with  $L \leq U$ . The *maximum-density segment* problem takes  $A$ ,  $L$ , and  $U$  as input and asks for a segment of  $A$  with the largest possible density among those of width at least  $L$  and at most  $U$ .

In its most basic form, the sequence  $A$  corresponds to the given DNA sequence, where  $a_i = 1$  if the corresponding nucleotide in the DNA sequence is G or C; and  $a_i = 0$  otherwise. In the work of Huang, sequence entires took on values of  $p$  and  $1 - p$  for some real number  $0 \leq p \leq 1$ . More generally, we can look for regions where a given set of patterns occur very often. In such applications,  $a_i$  could be the relative frequency that the corresponding DNA character appears in the given patterns. Further natural applications of this problem can be designed for sophisticated sequence analyses such as mismatch density [28], ungapped local alignments [1], and annotated multiple sequence alignments [31].

Nekrutendo and Li [25], and Rice, Longden and Bleasby [26] employed algorithms for the case where  $L = U$ . This case is trivially solvable in  $O(n)$  time. More generally, when  $L \neq U$ , the problem is trivially solvable in  $O(n(U - L + 1))$  time. Huang [17] studied the case where  $U = n$ , i.e., there is effectively no upper bound on the width of the desired maximum-density segments. He observed that an optimal segment exists with width at most  $2L - 1$ . Therefore, this case is equivalent to the case with  $U = 2L - 1$  and can be solved in  $O(nL)$  time in a straightforward manner. Recently, Lin, Jiang, and Chao [21] gave an  $O(n \log L)$ -time algorithm for this case based on right-skew partitions of a sequence.

Other related work include algorithms for the problem of computing a segment  $\langle a_i, \dots, a_j \rangle$  with a maximum sum  $a_i + \dots + a_j$  instead of a maximum density. Bentley [3] gave an  $O(n)$ -time algorithm for the case where  $L = 0$  and  $U = n$ .

Within the same linear time complexity, Huang [17] solved the case with arbitrary  $L$  and  $U = n$ . More recently, Lin, Jiang, and Chao [21] solved the case with arbitrary  $L$  and  $U$ .

In this paper, we report the following new results:

- Case 1:  $U = n$  (or equivalently,  $U = 2L - 1$ ). The maximum-density segment problem can be solved in  $O(n)$  time. This result exploits a non-nesting structure of locally optimal segments to improve upon the algorithm of Lin, Jiang, and Chao [21].
- Case 2:  $U$  and  $L$  are arbitrary. The maximum-density segment problem can be solved in  $O(n + n \log(U - L + 1))$  time.

We can generalize these two new results in a weighted variant of the problem on an input sequence  $A$  of  $n$  objects. Each object is represented by a pair of two real numbers  $(a_i, w_i)$  for  $i = 1, \dots, n$ , with  $w_i > 0$  denoting the *width*. With these definitions, the *density* of a segment  $\langle a_i, \dots, a_j \rangle$  becomes  $(\sum_{i \leq k \leq j} a_k) / (\sum_{i \leq k \leq j} w_k)$ . The width constraint now requires that  $L \leq w_i + \dots + w_j \leq U$ . We can solve this weighted variant with the same running times as in Case 1 with  $w_i > 0$  and in Case 2 with  $w_i \geq 1$ , respectively. Note that computationally, this weighted variant can be used to compress a real number sequence  $A$  to reduce its density analysis time in practice or theory.

The remainder of this paper is organized as follows. Section 2 introduces some notation and definitions. In Section 3, we carefully review the previous work of Lin, Jiang and Chao [21], in which they introduce the concept of right-skew partitions. Our main results are presented in Section 4, and we discuss the generalization of these results to the weighted variant in Section 5. We conclude the paper with some open problems in Section 6.

## 2 Notation and Preliminaries

Recall that  $A = \langle a_1, a_2, \dots, a_n \rangle$  denotes the input sequence of real numbers. We let  $A(i, j)$  denote the segment  $\langle a_i, \dots, a_j \rangle$ ,  $w(i, j) = j - i + 1$  the *width* of  $A(i, j)$ , and  $\mu(i, j)$  the density of  $A(i, j)$ . We note that the prefix sums of the input sequence can be precomputed in  $O(n)$  time. With these, a value  $\mu(i, j)$  can be computed in  $O(1)$  time, as

$$\mu(i, j) = \left( \sum_{1 \leq k \leq j} a_k - \sum_{1 \leq k \leq i-1} a_k \right) / w(i, j).$$

## 3 Right-Skew Segments

Lin, Jiang and Chao [21] define segment  $A(i, k)$  to be *right-skew* if and only if for all  $i \leq j < k$ ,  $\mu(i, j) \leq \mu(j + 1, k)$ . They prove that every  $A$  can be uniquely partitioned into right-skew segments  $A_1 A_2 \dots A_m$  such that  $\mu(A_x) > \mu(A_y)$  for

any  $x < y$ . They call this decomposition the *decreasingly right-skew partition* of  $A$ .

If  $A(i, k)$  is not right-skew, its decomposition must consist of the right-skew segment  $A(i, j)$  for some  $i \leq j < k$ , followed by the unique partition of  $A(j+1, k)$ . Because of this common structure, the decreasing right-skew partitions for all  $A(i, n)$  can be simultaneously represented by keeping a *right-skew pointer*,  $p[i]$  for each  $1 \leq i \leq n$ , where  $A(i, p[i])$  is the first right-skew segment for the decomposition of  $A(i, n)$ . They implicitly use dynamic programming to construct all such right-skew pointers in  $O(n)$  time.

In order to find a maximum-density segment of width at least  $L$ , they proceed by independently searching for the “good partner” of each index  $i$ . The good partner of  $i$  is the index  $j$  that maximizes  $\mu(i, j)$  while satisfying  $w(i, j) \geq L$ . In order to find each good partner, they make use of the following three lemmas.

**Lemma 1 (Atomic).** *Let  $B, C$  and  $D$  be three real sequences with  $\mu(B) < \mu(C) < \mu(D)$ . Then  $\mu(BC) < \mu(BCD)$ .*

**Lemma 2 (Bitonic).** *Let  $B$  be a real number sequence and  $C_1C_2 \cdots C_m$  the decreasingly right-skew partition of a sequence  $C$  which immediately follows  $B$ . Let  $\mu(BC_1C_2 \cdots C_k) = \max\{\mu(BC_1C_2 \cdots C_i) \mid 0 \leq i \leq m\}$ . Then  $\mu(BC_1C_2 \cdots C_i) > \mu(BC_1C_2 \cdots C_{i+1})$  if and only if  $i \geq k$ .*

**Lemma 3.** *Given a real number sequence  $B$ , let  $C$  denote the shortest segment of  $B$  with width at least  $L$  realizing the maximum density. Then the width of  $C$  is at most  $2L - 1$ .*

Without any upper bound on the desired segment length, the consequence of these lemmas is an  $O(\log L)$ -time algorithm for finding a good partner for arbitrary index  $i$ . Since only segments of width  $L$  or greater are of interest, the segment  $A(i, i + L - 1)$  must be included. Lin, Jiang and Chao [21] make use of the decreasingly right-skew partition of  $A(i + L, n)$  when searching for the good partner of  $i$ . If part of a right-skew segment improves the density of a candidate segment, then Lemma 1 assures that the entire right-skew segment should be included ( $C$  represents part of a complete right-skew segment  $CD$  in the statement of the lemma). Therefore, the good partner for  $i$  must be  $i + L - 1$  or else the rightmost index of one of the right-skew segments from the partition of  $A(i + L, n)$ . Lemma 2 shows that the inclusion of each successive right-skew segment leads to a bitonic sequence of densities, thus binary search can be used to locate the good partner. Finally, Lemma 3 assures that at most  $L$  right-skew segments need be considered for inclusion, and thus the binary search for a given  $i$  runs in  $O(\log L)$  time. The result is an  $O(n \log L)$  algorithm for arbitrary  $L$  and  $U = n$ .

## 4 Improved Algorithms

Our results make use of decreasingly right-skew partitions, as reviewed in Section 3. Our improvements are based upon the following observation. An exact

good partner for an index  $i$  need not be found if it can be determined that such a partner would result in density no greater than that of a segment already considered. This observation allows us to replace the binary searches used by Lin, Jiang and Chao [21], at cost of  $O(\log L)$  time each, with sequential searches that result in an *amortized* cost of  $O(1)$  time each. Before developing our complete algorithms, we introduce the sweep-line data structure which manages the search for good partners.

#### 4.1 A Sweep-Line Data Structure

Our data structure augments the right-skew pointers for a given interval with additional information used to speed up searches for good partners. In order to achieve improved efficiency, the structure supports searches limited in two ways:

1. The structure can be used to find matches for an arbitrary collection of values for  $i$ , however the queries must be made in decreasing order.
2. When asked to find the match for a left index, the structure will only find the true good partner in the case that the good partner has index less than or equal to all previously returned indices.

The data structure contains the following information, relative to fixed parameters  $1 \leq x \leq y \leq n$ :

1. A (static) array,  $p[k]$  for  $x \leq k \leq y$ , where  $A(k, p[k])$  is the right-skew segment starting the decreasingly right-skew partition of  $A(k, y)$ .
2. A (static) sorted list,  $S[k]$ , for each  $x \leq k \leq y$ , containing all indices  $j$  for which  $p[j] = k$ .
3. Two indices  $\ell$  and  $r$  (for “left” and “right”), whose values are non-increasing as the algorithm progresses.
4. A variable,  $b$  (for “bridge”), which is the minimum index such that  $\ell \leq b \leq r \leq p[b]$ .

The data structure is initialized with procedure `Initialize( $x, y$ )` for  $1 \leq x \leq y \leq n$ , as defined in Figure 1. An example of an initialized structure is given in Figure 2. Two other supported operations are given in Figures 3 and 4.

**Lemma 4 (Nesting).** *There cannot exist indices  $j$  and  $k$  such that  $j < k \leq p[j] < p[k]$ .*

*Proof.* For contradiction, assume that  $j$  is the maximum such value achieving a violation. Consider the point when  $p[j]$  is determined in `Initialize`. The value  $p[j]$  is initially set equal to  $j$  at line 3, and is increased by each execution of line 5. We consider the first time that  $j < k \leq p[j] < p[k]$ . Initially,  $p[j] = j$ , so the violation must be created at line 5. Immediately before that line, it must be that  $p[j] < k$  yet  $k \leq p[p[j] + 1] < p[k]$ . If  $p[j] + 1 < k \leq p[p[j] + 1] < p[k]$ , this would be a contradiction to  $j < p[j] + 1$  being the maximum violation of the lemma. Otherwise, it must be that  $p[j] + 1 = k$ , but then  $p[p[j] + 1] = p[k] \not< p[k]$ , leading to another contradiction. Therefore, no such violation can occur.  $\square$

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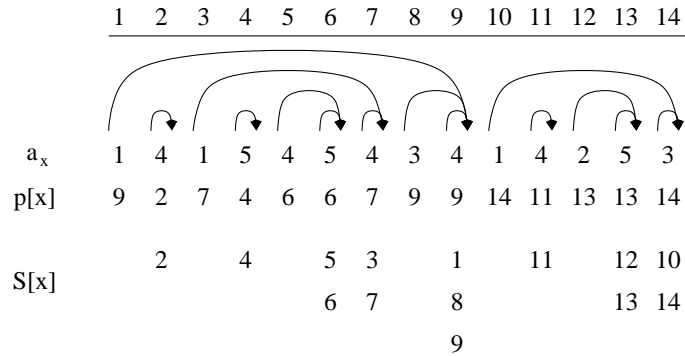
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procedure Initialize( $x, y$ )                                assumes  $1 \leq x \leq y \leq n$ 
1   for  $i \leftarrow y$  downto  $x$  do
2      $S[i] \leftarrow \emptyset$ 
3      $p[i] \leftarrow i$ 
4     while ( $p[i] < y$ ) and  $\mu(i, p[i]) \leq \mu(i, p[p[i] + 1])$  do
5        $p[i] \leftarrow p[p[i] + 1]$ 
6     end while
7     Insert  $i$  at beginning of  $S[p[i]]$ 
8   end for
9    $\ell \leftarrow y; r \leftarrow y; b \leftarrow y$ 

```

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**Fig. 1.** Data structure's Initialize( $x, y$ ) operation.



**Fig. 2.** Example of data structure after Initialize(1, 14).

**Lemma 5.** *If  $b$  is the minimum value satisfying  $\ell \leq b \leq r \leq p[b]$ , then  $A(b, p[b])$  is the segment of the decreasingly right-skew decomposition of  $A(\ell, y)$  which contains  $a_r$ .*

*Proof.* Assume  $b$  achieves such a minimum. The decomposition of  $A(\ell, y)$  will equal  $A(\ell, p[\ell])$ ,  $A(p[\ell] + 1, p[p[\ell] + 1])$ , and so on, until reaching right endpoint  $y$ . We claim that  $A(b, p[b])$  must be part of that decomposition. If not, there must be some other  $A(m, p[m])$  with  $m < b \leq p[m]$ . By Lemma 4, it must be that  $p[m] \geq p[b]$ , but such an  $m$  would violate the minimality of  $b$ .  $\square$

**Lemma 6.** *Whenever line 1 of FindMatch is evaluated,  $b$  is the minimum value satisfying  $\ell \leq b \leq r \leq p[b]$ .*

*Proof.* We show this by induction over time. When initialized,  $\ell = b = r = p[b] = y$ , and thus  $b$  is the only satisfying value. The only time this invariant can be broken is when the value of  $\ell$  or  $r$  changes.  $\ell$  is changed only when decremented at line 2 of DecreaseI. Since it still remains that  $\ell \leq b \leq r \leq p[b]$ , the only possible violation of the invariant is if new index  $\ell$  satisfies  $\ell \leq r \leq p[\ell]$ . This is exactly the condition handled by lines 3–4.

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procedure DecreaseI( $i$ )
1   while ( $w(i, \ell - 2) \geq L$ ) and ( $\ell - 2 \geq x$ ) do
2      $\ell \leftarrow \ell - 1$ 
3     if  $p[\ell] \geq r$  then
4        $b = \ell$ 
5     end if
6   end while

```

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**Fig. 3.** Data structure's `DecreaseI( $i$ )` operation.

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procedure FindMatch( $i$ )
1   while ( $r \geq \ell$ ) and ( $\mu(i, b - 1) > \mu(i, p[b])$ ) do
2      $r \leftarrow b - 1$ 
3     if ( $r \geq \ell$ ) then
4       find minimum  $k \in S[r]$  such that  $k \geq \ell$ 
5        $b \leftarrow k$ 
6     end if
7   end while
8   return  $r$ 

```

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**Fig. 4.** Data structure's `FindMatch( $i$ )` operation.

Secondly, we note that  $r$  is modified only at line 2 of `FindMatch`. Immediately before this line is executed, we consider all  $k$  such that  $\ell \leq k < b$ , and ask where  $p[k]$  might lie. By Lemma 4, it cannot be the case that  $b \leq p[k] < p[b]$ . If  $p[k] \geq p[b] \geq r$ , then  $k$  would violate the minimality of  $b$  assumed at line 1. Therefore, it must be that any  $k$  with  $\ell \leq k < b$  has  $p[k] \leq b - 1$ . After  $r$  is set to  $b - 1$ , we ask what values  $k$  satisfy  $\ell \leq k \leq r \leq p[k]$ . The only possibility will be those  $k$  for which  $p[k] = b - 1$ .  $S[b - 1]$  contains exactly those values of  $k$ , and so lines 4–5 restore the invariant regarding  $b$ .  $\square$

**Lemma 7.** *For a given call to `FindMatch( $i$ )`, let  $m_0$  be the most recently returned value from `FindMatch`, or  $y$  if this is the first such call. Let  $A(i, m)$  be a maximum-density segment that starts with  $i$ , has width at least  $L$ , and with  $m \in [x, y]$ . Then `FindMatch( $i$ )` returns the value  $\min(m, m_0)$  so long as `DecreaseI( $i$ )` was executed immediately prior.*

*Proof.* Since we are interested in segments of width at least  $L$  ending in  $[x, y]$ , any candidate segment must include interval  $A(i, k)$  where  $k$  is the minimum value satisfying both  $k \geq x$  and  $w(i, k) \geq L$ . Line 2 of the procedure `DecreaseI` ensures that variable  $\ell = k + 1$  upon exit. As discussed in Section 3, the optimal such  $m$  must either be  $k$  or else among the right endpoints of the right-skew segments in the decomposition of  $A(\ell, y)$ .

Upon entering `FindMatch`,  $r = m_0$ , and by Lemmas 5–6,  $A(b, p[b])$  is the right-skew segment containing  $a_r$  in the decomposition of  $A(\ell, y)$ . If  $\mu(i, b-1) \leq \mu(i, p[b])$ , the good partner must have index at least  $p[b] \geq r$ , by Lemma 2. In this case, the while loop is never entered, and the procedure returns  $m_0 = \min(m, m_0)$ .

In any other case, the while loop of line 1, combined with Lemmas 2 and 6, assures that the returned value of  $r$  is precisely  $m = \min(m, m_0)$ .  $\square$

**Lemma 8.** *The data structure supports its operations with amortized running time of  $O(y - x + 1)$  for `Initialize`( $x, y$ ), and  $O(1)$  for each of `DecreaseI`( $i$ ) and `FindMatch`( $i$ ).*

*Proof.* With the exception of lines 2, 7 and 9, the initialization procedure is simply a restatement of the algorithm given by Lin, Jiang and Chao [21] for constructing the right-skew pointers. An  $O(y - x + 1)$ -time worst case bound was proven by those authors.

To account for `DecreaseI` we note that  $\ell$  is initialized to value  $y$  at line 9 of `Initialize`, is modified only when decremented at line 2 of `DecreaseI`, and remains at least  $x + 1$  due to line 1 of `DecreaseI`. Therefore the loop executes  $O(y - x + 1)$  times and this cost can be amortized against the initialization cost. An  $O(1)$  amortized cost can account for checking the initial test condition before entering the loop.

In analyzing the cost of `FindMatch` we note that variable  $r$  is initialized to value  $y$  at line 9 of `Initialize`. By Lemma 6,  $b \leq r \leq p[b]$ , and so we note that the execution of line 2 of `FindMatch` always results in a strict decrease in the value of  $r$ . Therefore, the while loop of that routine executes  $O(y - x + 1)$  times. The only step within that loop which cannot be bounded by  $O(1)$  in the worst case is that of line 4. However, since each  $k$  appears in list  $S[r]$  for a distinct value of  $r$ , the overall cost associated with line 4 is bounded by  $O(y - x + 1)$ . This, and the remaining cost of the while loop, can be amortized against the initialization cost.  $\square$

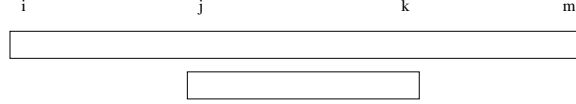
## 4.2 Maximum-Density Segment with Width at Least $L$

In this section, we consider the problem of finding a segment with the maximum possible density among those of width at least  $L$ . We present a linear time algorithm which makes use of the data structure developed in Section 4.1. The key to the correctness of the algorithm is the following lemma.

**Lemma 9.** *For a given  $j$ , assume  $A(j, k)$  is a maximum-density segment, of those starting with index  $j$  and having width at least  $L$ . For a given  $i < j$ , assume  $A(i, m)$  is a maximum-density segment, of those starting with index  $i$  and having width at least  $L$ . If  $m > k$ , then  $\mu(j, k) \geq \mu(i, m)$ .*

*Proof.* A typical such configuration is shown in Figure 5. Since both  $A(j, k)$  and  $A(j, m)$  have width at least  $L$ , the optimality of  $A(j, k)$  guarantees that  $\mu(j, k) \geq \mu(j, m)$ . This implies that  $\mu(j, k) \geq \mu(j, m) \geq \mu(k + 1, m)$ . Since both





**Fig. 5.** Segments in proof of Lemma 9.

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1 Call Initialize(1, n) to create data structure
2  $i_0 \leftarrow$  maximum index such that  $w(i_0, n) \geq L$ 
3 for  $i \leftarrow i_0$  downto 1 do
4   DecreaseI( $i$ )
5    $g[i] \leftarrow$  FindMatch( $i$ )
6 end for
7 return ( $k, g[k]$ ) which maximizes  $\mu(k, g[k])$  for  $1 \leq k \leq i_0$ 

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**Fig. 6.** Algorithm for finding maximum-density segment with width at least  $L$ .

$A(i, k)$  and  $A(i, m)$  have width at least  $L$ , the optimality of  $A(i, m)$  guarantees that  $\mu(i, m) \geq \mu(i, k)$ , which in turn implies  $\mu(k + 1, m) \geq \mu(i, m) \geq \mu(i, k)$ . Combining these inequalities,  $\mu(j, k) \geq \mu(j, m) \geq \mu(k + 1, m) \geq \mu(i, m)$ , thus proving the claim that  $\mu(j, k) \geq \mu(i, m)$ .  $\square$

**Theorem 1.** *A maximum-density segment of  $A = \langle a_1, a_2, \dots, a_n \rangle$  of those with width at least  $L$  can be found in  $O(n)$  time.*

*Proof.* The algorithm is given in Figure 6. The correctness is a direct result of Lemmas 7 and 9. The running time bound is a direct consequence of Lemma 8.  $\square$

### 4.3 Maximum-Density Segment with Width at Least $L$ , at Most $U$

In this section, we consider the problem of finding an interval with the maximum possible density among those of width at least  $L$  and at most  $U$ . When  $U \geq 2L - 1$ , the upper bound is inconsequential by Lemma 3, and the linear-time algorithm from the previous section suffices. For  $L < U < 2L - 1$ , however, there is a subtle problem if trying to apply the previous algorithm directly.

Without any upper bound on the width, a good partner for index  $i$  was chosen in the range  $A(p_i, n)$  where  $p_i$  is the minimum index such that  $w(i, p_i) \geq L$ . The decreasingly right-skew decomposition of  $A(p_i + 1, n)$  was used in the search for the good partner. In similar spirit, when later searching for a good partner for  $i - 1$ , the decreasingly right-skew decomposition of  $A(p_{i-1} + 1, n)$  was used. The beauty of the framework was the fact that the right-skew pointers simultaneously represent the decomposition for all segments of the form  $A(p + 1, n)$ , for fixed endpoint  $n$ . Furthermore, Lemma 1 ensured that the right-skew segments could be treated atomically.

With an upper bound on the width, however, an atomic right-skew segment from the decomposition of  $A(p_i + 1, n)$  may violate the upper limit. It appears that the more relevant decomposition, for a given  $i$ , is that of  $A(p_i + 1, q_i)$  where  $q_i$  the maximum index with  $w(i, q_i) \leq U$ . Sadly, it is not apparent whether the structure of that decomposition can be reused as the right end of the interval changes for other values of  $i$ .

In the remainder of this section, we present an  $O(n + n \log(U - L + 1))$ -time algorithm in the setting with both a lower bound and upper bound on the segment width. For a given index  $i$ , we know that the good partner lies in a range  $A(p_i, q_i)$ , as defined above. Rather than directly compute the decreasingly right-skew partition of  $A(p_i + 1, q_i)$  for each  $i$ , we will compute decompositions for a collection of smaller blocks which exactly cover the range  $A(p_i, q_i)$  yet can be reused for other values of  $i$ . We build a sweep-line data structure independently for each block and make use of a lemma which guarantees that we find the global solution to the problem, even if we do not find the true good partner for each  $i$ .

For ease of notation, we assume, without loss of generality, that the overall sequence  $A$  is padded with values so that it has length  $n$  which is a power of two. We consider  $n$  blocks of size 1,  $n/2$  blocks of size 2,  $n/4$  blocks of size 4, and so on until  $n/2^\beta$  blocks of size  $2^\beta$ , where  $\beta = \lfloor \log_2(U - L + 1) \rfloor$ . Specifically, we define block  $B_{j,k} = A(1 + j * 2^k, (j + 1) * 2^k)$  for all  $0 \leq k \leq \beta$  and  $0 \leq j < n/2^k$ . We begin with the following lemma.

**Lemma 10.** *For any interval  $A(p, q)$  with cardinality at most  $U - L + 1$ , we can compute, in  $O(1 + \beta)$  time, a collection of  $O(1 + \beta)$  disjoint blocks such that  $A(p, q)$  equals the union of the blocks.*

*Proof.* The algorithm `CollectBlocks` is given in Figure 7, and a sample result is shown in Figure 8. We leave it as an exercise to verify the claim.  $\square$

Before presenting the main result for this section, we need the following variant of Lemma 9.

**Lemma 11.** *For a given  $j$ , assume  $A(j, k)$  is a maximum-density segment, of those starting with index  $j$ , having width at least  $L$ , and ending with index in range  $[x, y]$ . For a given  $i < j$ , assume  $A(i, m)$  is a maximum-density segment, of those starting with index  $i$ , having width at least  $L$ , and ending with index in range  $[x, y]$ . If  $m > k$  then  $\mu(j, k) \geq \mu(i, m)$ .*

*Proof.* Identical to Lemma 9, as both  $k$  and  $m$  lie in range  $[x, y]$ .  $\square$

**Theorem 2.** *A maximum-density segment of  $A = \langle a_1, a_2, \dots, a_n \rangle$  of those with width at least  $L$  and at most  $U$  can be found in  $O(n + n \log(U - L + 1))$  time.*

*Proof.* The algorithm is given in Figure 9. First, we discuss the correctness. Assume that the global maximum is achieved by  $A(i, m)$ . We must simply show that this pair, or one with equal density, was considered at line 14. Based on the width constraints, it must be that  $p \leq m \leq q$ , for  $p$  and  $q$  as defined in lines 9–10. By Lemma 10,  $m$  must lie in some  $B_{j,k}$  returned by `CollectBlocks(p, q)`.

---

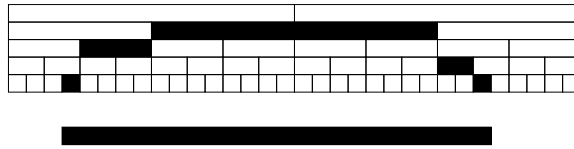
```

procedure CollectBlocks( $p, q$ )
1    $s \leftarrow p; k \leftarrow 0$ 
2   while ( $2^k + s - 1 \leq q$ ) do
3     while ( $2^{k+1} + s - 1 \leq q$ ) do
4        $k \leftarrow k + 1$ 
5     end while
6      $j \leftarrow \lceil s/2^k \rceil - 1$ 
7     Add block  $B_{j,k}$  to the collection
8      $k \leftarrow k + 1$ 
9   end while
10  while ( $s \leq q$ ) do
11    while ( $2^k + s - 1 > q$ ) do
12       $k \leftarrow k - 1$ 
13    end while
14     $j \leftarrow \lceil s/2^k \rceil - 1$ 
15    Add block  $B_{j,k}$  to the collection
16     $k \leftarrow k - 1$ 
17  end while

```

---

**Fig. 7.** Algorithm for finding collection of blocks to cover an interval.



**Fig. 8.** A collection of blocks for a given interval.

Because  $\mu(i, m)$  is a global maximum, the combination of Lemmas 7 and 11 assures us that `FindMatch` at line 13 will return  $m$  (or an index achieving the same density).

We conclude by showing that the running time is  $O(n + n\beta)$ . Notice that for a fixed  $k$ , blocks  $B_{j,k}$  for  $0 \leq j < n/2^k - 1$  comprise a partition of the original input  $A$ , and thus the sum of their cardinalities is  $O(n)$ . Therefore, for a fixed  $k$  lines 3–5 run in  $O(n)$  time by Lemma 8, and overall lines 2–6 run in  $O(n\beta)$  time. Lines 9–10 can be accomplished in  $O(1)$  time as  $p = i + L - 1$  and  $q = i + U - 1$  by definition. Each call to `CollectBlocks` from line 11 runs in  $O(1 + \beta)$  time by Lemma 10, and produces  $O(1 + \beta)$  blocks. Therefore, the body of that loop, lines 12–17, executes  $O(n + n\beta)$  times over the course of the entire algorithm.

Finally, we must account for the time spent in all calls to `DecreaseI` and `FindMatch` from lines 12–13. Rather than analyze these costs chronologically, we account for these calls by considering each block  $B_{j,k}$  over the course of the algorithm. For a given block, the parameter values sent to `DecreaseI` are indeed strictly decreasing. Therefore by Lemma 8, each of these calls has an amortized

---

```

1   $\beta \leftarrow \lfloor \log_2(U - L + 1) \rfloor$ ;  $\mu_{max} \leftarrow -\infty$ 
2  for  $k \leftarrow 0$  to  $\beta$  do
3      for  $j \leftarrow 0$  to  $n/2^k - 1$  do
4           $B_{j,k} \leftarrow \text{Initialize}(1 + j * 2^k, (j + 1) * 2^k)$ 
5      end for
6  end for
7   $i_0 \leftarrow$  maximum index such that  $w(i_0, n) \geq L$ 
8  for  $i \leftarrow i_0$  downto 1 do
9       $p \leftarrow$  minimum index such that  $w(i, p) \geq L$ 
10      $q \leftarrow$  maximum index such that  $w(i, q) \leq U$ 
11     foreach  $B_{j,k}$  in  $\text{CollectBlocks}(p, q)$  do
12          $\text{DecreaseI}(i)$ 
13          $temp \leftarrow \text{FindMatch}(i)$ 
14         if  $\mu(i, temp) > \mu_{max}$  then
15              $\mu_{max} \leftarrow \mu(i, temp)$ 
16             record achieving endpoints,  $(i, temp)$ 
17         end if
18     end foreach
19 end for

```

---

**Fig. 9.** Algorithm for maximum-density segment with width at least  $L$  and at most  $U$ .

cost of  $O(1)$ , where that cost is amortized over the initialization costs for the blocks.  $\square$

## 5 Extensions to the Weighted Case

We can generalize the maximum-density segment problem to an input  $A$  of  $n$  objects, where each object is represented by a pair of two real numbers  $(a_i, w_i)$  for  $i = 1, \dots, n$ , with  $w_i > 0$ . We use the term “width” for  $w_i$  rather than “weight” to avoid possible confusion in context, as this parameter appears as the denominator in the following “density” formula:

$$\mu(i, j) = \left( \sum_{i \leq k \leq j} a_k \right) / \left( \sum_{i \leq k \leq j} w_k \right).$$

We note that the prefix sums can separately be computed for  $a_k$  and  $w_k$  in  $O(n)$  time, after which we can compute  $w(i, j)$  in  $O(1)$  time as

$$\left( \sum_{1 \leq k \leq j} w_k - \sum_{1 \leq k \leq i-1} w_k \right),$$

and  $\mu(i, j)$  as described in Section 2. In this setting, we now ask whether we can find the segment with maximum possible density of those having  $L \leq w(i, j) \leq U$ . We offer the following two theorems.

**Theorem 3.** *A maximum-density segment of  $A = \langle (a_1, w_1), \dots, (a_n, w_n) \rangle$  of those with width at least  $L$  can be found in  $O(n)$  time.*

**Theorem 4.** *If  $w_i \geq 1$  for all  $i$ , then a maximum-density segment of  $A = \langle (a_1, w_1), (a_2, w_2), \dots, (a_n, w_n) \rangle$  of those with width at least  $L$  and at most  $U$  can be found in  $O(n + n \log(U - L + 1))$  time.*

The algorithms as presented in Section 4 can be used essentially unchanged with the new computations for  $w(i, j)$  and  $\mu(i, j)$ . The only additional algorithmic change required is that for a given left index  $i$ , we must be able to calculate the effective range for the good partner search. Namely, we must find  $p$  which is the minimum index satisfying  $w(i, p) \geq L$  and  $q$  which is the maximum index satisfying  $w(i, q) \leq U$ . These values can be precomputed for all  $i$  in  $O(n)$  overall time by sweeping a pair of indices across the full sequence.

As far as the correctness, we note that the facts about right-skew segments provided by Lin, Jiang and Chao [21] do not in any way involve the width of segments, and so those results are unaffected by the width parameters. Those parameters only have effect once lower and upper bounds on the width are applied to the problem. All of our proofs from Section 4 were written so as to be valid with this weighted variant.

The running time bounds for the algorithms remain intact in this weighted version as well. The caveat that  $w_i \geq 1$  from Theorem 4 is needed to guarantee that the cardinality of the interval  $[p, q]$  is at most  $(U - L + 1)$ , so as to apply Lemma 10.

## 6 Conclusions

We have shown that if  $U = n$  (or equivalently,  $U = 2L - 1$ ), we can solve the maximum-density segment problem in  $O(n)$  time. If  $U$  and  $L$  are arbitrary, we can solve the problem in  $O(n + n \log(U - L + 1))$  time. These results hold for both the unweighted and weighted versions of the problem. Recently, the techniques of this paper have been expanded by the authors to achieve linear time when  $U$  and  $L$  are arbitrary; details will appear in a subsequent paper.

A further research direction is to generalize the input sequence  $A$  to an array of dimension two or higher. This generalization conceivably may have applications to image analysis in bioinformatics and other fields.

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## References

1. N. N. Alexandrov and V. V. Solovyev. Statistical significance of ungapped sequence alignments. In *Proceedings of Pacific Symposium on Biocomputing*, volume 3, pages 461–470, 1998.

2. G. Barhardi. Isochores and the evolutionary genomics of vertebrates. *Gene*, 241:3–17, 2000.
3. J. L. Bentley. *Programming Pearls*. Addison-Wesley, Reading, MA, 1986.
4. G. Bernardi and G. Bernardi. Compositional constraints and genome evolution. *Journal of Molecular Evolution*, 24:1–11, 1986.
5. B. Charlesworth. Genetic recombination: patterns in the genome. *Current Biology*, 4:182–184, 1994.
6. L. Duret, D. Mouchiroud, and C. Gautier. Statistical analysis of vertebrate sequences reveals that long genes are scarce in GC-rich isochores. *Journal of Molecular Evolution*, 40:308–371, 1995.
7. A. Eyre-Walker. Evidence that both G+C rich and G+C poor isochores are replicated early and late in the cell cycle. *Nucleic Acids Research*, 20:1497–1501, 1992.
8. A. Eyre-Walker. Recombination and mammalian genome evolution. *Proceedings of the Royal Society of London Series B, Biological Science*, 252:237–243, 1993.
9. C. A. Fields and C. A. Soderlund. gm: a practical tool for automating DNA sequence analysis. *Computer Applications in the Biosciences*, 6:263–270, 1990.
10. J. Filipski. Correlation between molecular clock ticking, codon usage fidelity of DNA repair, chromosome banding and chromatin compactness in germline cells. *FEBS Letters*, 217:184–186, 1987.
11. M. P. Francino and H. Ochman. Isochores result from mutation not selection. *Nature*, 400:30–31, 1999.
12. S. M. Fullerton, A. B. Carvalho, and A. G. Clark. Local rates of recombination are positively correlated with GC content in the human genome. *Molecular Biology and Evolution*, 18(6):1139–1142, 2001.
13. P. Guldborg, K. Gronbak, A. Aggerholm, A. Platz, P. thor Straten, V. Ahrenkiel, P. Hokland, and J. Zeuthen. Detection of mutations in GC-rich DNA by bisulphite denaturing gradient gel electrophoresis. *Nucleic Acids Research*, 26(6):1548–1549, 1998.
14. R. C. Hardison, D. Drane, C. Vandenberg, J.-F. F. Cheng, J. Mansverger, J. Tadie, S. Schwartz, X. Huang, and W. Miller. Sequence and comparative analysis of the rabbit alpha-like globin gene cluster reveals a rapid mode of evolution in a G+C rich region of mammalian genomes. *Journal of Molecular Biology*, 222:233–249, 1991.
15. W. Henke, K. Herdel, K. Jung, D. Schnorr, and S. A. Loening. Betaine improves the PCR amplification of GC-rich DNA sequences. *Nucleic Acids Research*, 25(19):3957–3958, 1997.
16. G. P. Holmquist. Chromosome bands, their chromatin flavors, and their functional features. *American Journal of Human Genetics*, 51:17–37, 1992.
17. X. Huang. An algorithm for identifying regions of a DNA sequence that satisfy a content requirement. *Computer Applications in the Biosciences*, 10(3):219–225, 1994.
18. K. Ikehara, F. Amada, S. Yoshida, Y. Mikata, and A. Tanaka. A possible origin of newly-born bacterial genes: significance of GC-rich nonstop frame on antisense strand. *Nucleic Acids Research*, 24(21):4249–4255, 1996.
19. R. B. Inman. A denaturation map of the 1 phage DNA molecule determined by electron microscopy. *Journal of Molecular Biology*, 18:464–476, 1966.
20. R. Jin, M.-E. Fernandez-Beros, and R. P. Novick. Why is the initiation nick site of an AT-rich rolling circle plasmid at the tip of a GC-rich cruciform? *The EMBO Journal*, 16(14):4456–4466, 1997.

21. Y. L. Lin, T. Jiang, and K. M. Chao. Algorithms for locating the length-constrained heaviest segments, with applications to biomolecular sequence analysis. *Journal of Computer and System Sciences*, 2002. To appear.
22. G. Macaya, J.-P. Thiery, and G. Bernardi. An approach to the organization of eukaryotic genomes at a macromolecular level. *Journal of Molecular Biology*, 108:237–254, 1976.
23. C. S. Madsen, C. P. Regan, and G. K. Owens. Interaction of CArG elements and a GC-rich repressor element in transcriptional regulation of the smooth muscle myosin heavy chain gene in vascular smooth muscle cells. *Journal of Biological Chemistry*, 272(47):29842–29851, 1997.
24. S.-i. Murata, P. Herman, and J. R. Lakowicz. Texture analysis of fluorescence lifetime images of AT- and GC-rich regions in nuclei. *Journal of Histochemistry and Cytochemistry*, 49:1443–1452, 2001.
25. A. Nekrutenko and W.-H. Li. Assessment of compositional heterogeneity within and between eukaryotic genomes. *Genome Research*, 10:1986–1995, 2000.
26. P. Rice, I. Longden, and A. Bleasby. EMBOSS: The European molecular biology open software suite. *Trends in Genetics*, 16(6):276–277, June 2000.
27. L. Scotto and R. K. Assoian. A GC-rich domain with bifunctional effects on mRNA and protein levels: implications for control of transforming growth factor beta 1 expression. *Molecular and Cellular Biology*, 13(6):3588–3597, 1993.
28. P. H. Sellers. Pattern recognition in genetic sequences by mismatch density. *Bulletin of Mathematical Biology*, 46(4):501–514, 1984.
29. P. M. Sharp, M. Averof, A. T. Lloyd, G. Matassi, and J. F. Peden. DNA sequence evolution: the sounds of silence. *Philosophical Transactions of the Royal Society of London Series B, Biological Sciences*, 349:241–247, 1995.
30. P. Soriano, M. Meunier-Rotival, and G. Bernardi. The distribution of interspersed repeats is nonuniform and conserved in the mouse and human genomes. *Proceedings of the National Academy of Sciences of the United States of America*, 80:1816–1820, 1983.
31. N. Stojanovic, L. Florea, C. Riemer, D. Gumucio, J. Slightom, M. Goodman, W. Miller, and R. Hardison. Comparison of five methods for finding conserved sequences in multiple alignments of gene regulatory regions. *Nucleic Acids Research*, 27:3899–3910, 1999.
32. N. Sueoka. Directional mutation pressure and neutral molecular evolution. *Proceedings of the National Academy of Sciences of the United States of America*, 80:1816–1820, 1988.
33. Z. Wang, E. Lazarov, M. O'Donnel, and M. F. Goodman. Resolving a fidelity paradox: Why *Escherichia coli* DNA polymerase II makes more base substitution errors in AT- compared to GC-rich DNA. *Journal of Biological Chemistry*, 2002. To appear.
34. K. H. Wolfe, P. M. Sharp, and W.-H. Li. Mutation rates differ among regions of the mammalian genome. *Nature*, 337:283–285, 1989.
35. Y. Wu, R. P. Stulp, P. Elfferich, J. Osinga, C. H. Buys, and R. M. Hofstra. Improved mutation detection in GC-rich DNA fragments by combined DGGE and CDGE. *Nucleic Acids Research*, 27(15):e9, 1999.
36. S. Zoubak, O. Clay, and G. Bernardi. The gene distribution of the human genome. *Gene*, 174:95–102, 1996.