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A Multiple Divide-and-Conquer (MDC) Algorithm for Optimal Alignments in Linear Space

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A MULTIPLE DIVIDE-AND-CONQUER (MDC) ALGORITHM FOR OPTIMAL ALIGNMENTS IN LINEAR SPACE

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ABSTRACT

This paper describes an algorithm for optimal sequence alignments in linear space. A new multiple divide-and-conquer technique is presented that leads to a linear space alignment algorithm which improves upon an existing algorithm by Myers and Miller.

1 Introduction

Dynamic programming algorithms are often used to find the similarities of sequences as well as to deliver the actual alignment of two sequences. Two kinds of alignments are used to compare sequences: local alignments and global alignments. The local alignments attempt to locate conserved regions, while the global alignments identify overall relationship between two sequences.

While dynamic programming algorithms are relatively time consuming, the space required is often the limiting factor when aligning long sequences. A linear space algorithm for computing maximal common subsequences, proposed by Hirschberg [1], was applied by Myers and Miller [2] to deliver optimal alignments in linear space. We have improved the Myers and Miller algorithm by introducing a multiple divide and conquer technique that reduces the algorithm's running time while maintaining its linear space property.

In the following sections, we use brackets [] to represent a matrix and parentheses () to represent a single entry in the matrix: $D[m,n]$ represents a matrix D, while $D(i,j)$ represents a single entry in the matrix D at the ith row and the jth column.

2 Dynamic Programming Algorithms

We first give a dynamic programming algorithm for global sequence alignments. Given two sequences $A = a_1a_2...a_m$ and $B = b_1b_2...b_n$, a cost, w, for k insertions or deletions is defined as $w(k) = (u * k + v)$, where $u \geq 0$ and $v \geq 0$. The minimum cost of aligning the two sequences is given in [3]:

$$D(i,j) = min \begin{cases} D(i-1,j-1) + c(b_i, a_j), \\ P(i,j), \\ Q(i,j). \end{cases} \qquad 0 < i \leq m, 0 < j \leq n$$

where

$$P(i,j) = min \begin{cases} D(i-1,j) + w(1), \\ P(i-1,j) + u. \end{cases}$$

$$Q(i,j) = min \begin{cases} D(i,j-1) + w(1), \\ Q(i,j-1) + u. \end{cases}$$

$$P(0,k) = Q(k,0) = D(k,0) = D(0,k) = w(k), \forall k > 0$$

and

$$c(b_i, a_j) = \begin{cases} \geq 0 & if \;\; b_i \neq a_j \\ \leq 0 & if \;\; b_i = a_j \end{cases}$$

The value $D(m, n)$ represents the minimum cost of aligning the two sequences.

To deliver the optimal alignment (that corresponds to the minimal cost), a traceback procedure is performed to find the actual alignment. A straightforward implementation of the traceback procedure requires $O(nm)$ space, thus limiting it to only short sequence alignments.

If only the minimum cost is needed and not the alignment, linear space is enough to do the calculation. As the value in position (i, j) depends only on values in three other positions, i.e., $(i, j-1)$, $(i-1, j-1)$ and $(i-1, j)$, one can do the calculation in a row by row fashion using only linear space (see [2] for details on the linear space cost only algorithm). This algorithm will be referred to later as the linear-space-cost-only algorithm.

The Hirschberg algorithm, applied by Myers and Miller to sequence alignments [2], is a divide-and-conquer algorithm designed to compute the alignment using linear space. The idea is to divide the first sequence into two halves A_1A_2 and then to locate the optimal point in the second sequence (which divides the second sequence into two parts B_1B_2) such that the optimal alignment is the concatenation of the optimal alignment of A_1 and B_1 and the optimal alignment of A_2 and B_2 (see Figure 1).

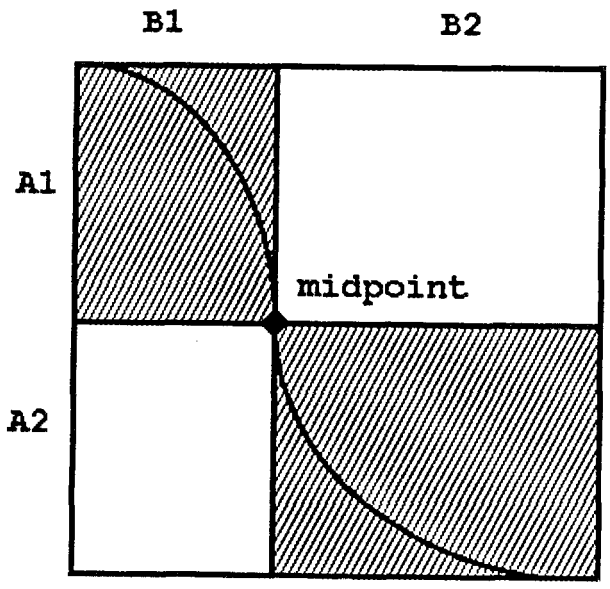


Figure 1. Divide and conquer.

The optimal alignment of two sequences can be thought of as a path in the cost matrix that starts at $D(0,0)$ and ends at $D(m,n)$. This path must cross the middle row (*midrow*) $i^* = \frac{m}{2}$. The problem is to find the point (*midpoint*) where the optimal path crosses the *midrow*.

Myers and Miller's algorithm uses the linear-space-cost-only algorithm to find the *midpoint*. First it calculates

- $DF(j)$ = the minimum cost of aligning $a_1a_2...a_{i^*}$ and $b_1b_2...b_j$
- $DR(j)$ = the minimum cost of aligning $a_{i^*+1}...a_{n-1}a_m$ and $b_{j+1}b_{j+2}...b_n$

where $0 \leq j \leq n$. Then it calculates

$$j^* = min_{j\in[0,n]}\{DF(j) + DR(n-j)\}.$$

(i^*, j^*) is the optimal *midpoint* (for a proof see [1]).

The optimal alignment is obtained by recursively finding the optimal alignment of the two subsequences before the *midpoint* and the optimal alignment of the two subsequences after the *midpoint*.

The actual algorithm is a bit more involved as it considers the types of the operations (replacement, delete, etc.) before and after the *midpoint* on the optimal path, and divides the problem accordingly.

3 A New Linear Space Alignment Algorithm

We first introduce a new technique to find the *midpoint*. We define a matrix $CROSS[m,n]$: $CROSS(i,j)$, when $i \geq \frac{m}{2}$, contains the column of the cost matrix where the optimal path that starts at $D(0,0)$ and ends at $D(i,j)$ crosses the *midrow*. $CROSS(i,j)$ is undefined for $i < \frac{m}{2}$. When both $D[m,n]$ and $CROSS[m,n]$ have been calculated, $D(m,j)$ contains the minimum cost of aligning $A = a_1a_2...a_m$ and $B = b_1b_2...b_j$, $0 \leq j \leq n$, and $CROSS(m,j)$ contains the column where the optimal path that starts at $(0,0)$ and ends at (m,j) crosses the *midrow*. In particular, $CROSS(m,n)$ contains the *midpoint*.

The calculation of $CROSS[m,n]$ is straightforward. Suppose we are calculating $D(i,j)$. The last operation in Figure 2 refers to the operation (i.e., a replacement, a deletion, or a insertion) that leads to $D(i,j)$. The path in Figure 2 refers to the optimal path that starts at $D(0,0)$ and ends at $D(i,j)$.

- If $(i = i^* + 1)$ then
  - $CROSS(i,j) = j$ if the last operation is a deletion,
  - $CROSS(i,j) = j - 1$ if the last operation is a replacement,
  - $CROSS(i,j) = CROSS(i,j-1)$ if the last operation is an insertion.
- else pass on the crossing-point information
  - $CROSS(i,j) = CROSS(i-1,j)$ if the last operation is a deletion,
  - $CROSS(i,j) = CROSS(i-1,j-1)$ if the last operation is a replacement,
  - $CROSS(i,j) = CROSS(i,j-1)$ if the last operation is an insertion.

Figure 2. Calculation of $CROSS(i,j)$ at $D(i,j)$.

Like $D[i,j]$, $CROSS[m,n]$ can be calculated easily in linear space. All we need is the value $CROSS(m,n)$. The cost is the added operation and the extra n space. We call the linear space cost only alignment algorithm with the added matrix $CROSS[m,n]$ the modified-linear-space-cost-only alignment algorithm.

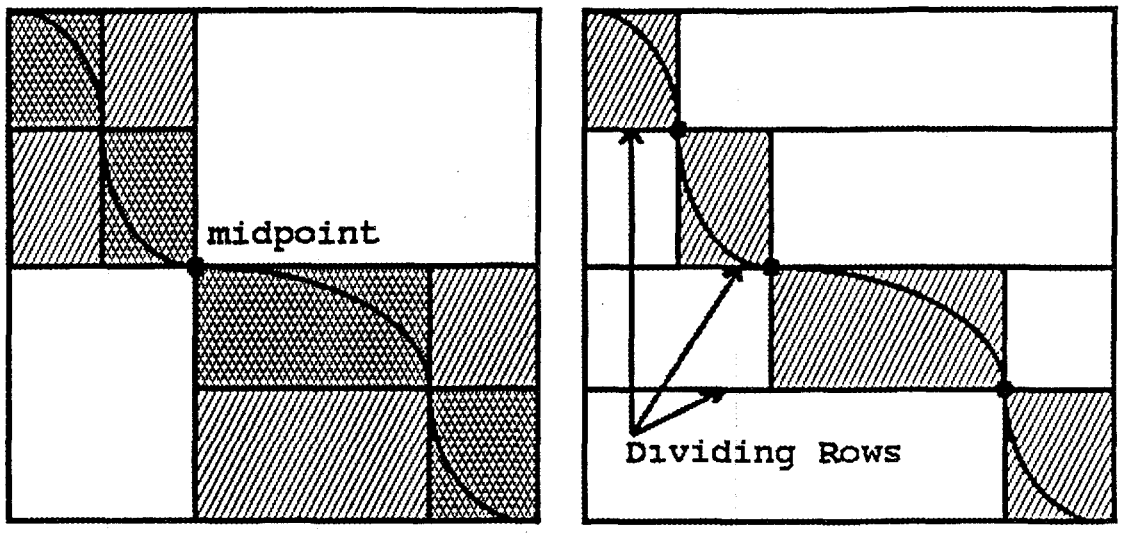
A natural extension of the above divide-and-conquer technique is to use more than one *dividing row*. The calculations of where the optimal path crosses the *dividing rows* are similar to that for *midrow*. Extra kn space is need to store the crossing information for k *dividing rows* .

The main MDC algorithm is outlined as follows: given two sequences,

- apply the modified-linear-space-cost-only alignment algorithm to find and save the crossing information at these k *dividing rows*,
- recursively divide each sequence into k subsequences according to the crossing information at these k *dividing rows* until the alignment is trivial to do,
- the optimal alignment is the concatenation of the optimal alignments of these k pairs of subsequences.

4 Analysis and Results

Let T_1 be the time of linear-space-cost-only algorithm. The total area of the calculation of the linear-space-cost-only algorithm is the cost matrix D. Using the Myers and Miller algorithm, after one recursion, the problem is divided into two subproblems whose total area is half of the cost matrix. In turn these two subproblems are divided into four subproblems whose total area is one fourth of the cost matrix, and so on (see Figure 3(a)).



(a) The Myers and Miller algorithm. (b) The MDC algorithm.

Figure 3. Divide and conquer.

So the approximate time T_2 for the Myers and Miller algorithm is

$$T_2 = T_1 * (1 + \frac{1}{2} + \frac{1}{4} + \cdots) \approx 2T_1$$

If four *dividing rows* are used in the MDC algorithm, each recursion divides a problem (or a subproblem) into four subproblems (see Figure 3(b)).

So the time of our algorithm T_3 is approximately

$$T_3 = T_1 * (1 + \frac{1}{4} + \frac{1}{4^2} + \cdots) \approx \frac{4}{3}T_1$$

In general, let d be the number of *dividing rows.* A problem is recursively divided into $s = d + 1$ subproblems, so T_3 is

$$T_3 \approx \frac{s}{s-1}T_1$$

This is only an estimate since the cost of the added operation is not taken into account. But as demonstrated below, the gain as a result of the introduction of the multiple divide-and-conquer technique is much more than the cost, resulting in substantial saving in the execution time.

To test the method, we used a simplified version, where $w(k) = u*k$. In the following table, MDC4, MDC8, and MDC16 refer to the MDC algorithm when $s = 4$, 8, or 16 respectively, and seq_len is the length of each of the two sequences. The algorithms were tested on a SUN SPARC 10 Workstation. We used a straightforward implementation of the algorithm. A refined version that reduces the cost of the newly introduced operation in the linear-space-cost-only algorithm will lead to a faster algorithm.

seq_len	Myers	MDC4	MDC8	MDC16
3500	0:34	0:29	0:25	0:23
7000	2:41	1:55	1:41	1:35
14000	9:13	7:45	7:07	6:21
28000	37:05	31:40	27:05	26:08

Table 2. Times (in minutes:seconds) of the linear space alignment algorithms

5 Conclusions

Sequence alignments using dynamic programming algorithms are demanding in both time and space, so efficient sequence alignment algorithms have been an active topic in computational biology. Here we have presented a multiple divide-and-conquer technique which improves the linear space alignment algorithm proposed by Myers and Miller. Still, aligning long sequences takes considerable time, so approximate algorithms which use prescreening methods such as dot matrix and k-tuple look tables, may be used together with this optimal dynamic programming algorithm to produce even more efficient systems.

6 Acknowledgments

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