Computing alignment plots efficiently

Peter Krusche and Alexander Tiskin*,
Dept. of Computer Science, University of Warwick, Coventry, CV4 7AL, UK

Abstract. Dot plots are a standard method for local comparison of biological sequences. In a dot plot, a substring to substring distance is computed for all pairs of fixed-size windows in the input strings. Commonly, the Hamming distance is used since it can be computed in linear time. However, the Hamming distance is a rather crude measure of string similarity, and using an alignment-based edit distance can greatly improve the sensitivity of the dot plot method. In this paper, we show how to compute alignment plots of the latter type efficiently. Given two strings of length $m$ and $n$ and a window size $w$, this problem consists in computing the edit distance between all pairs of substrings of length $w$, one from each input string. The problem can be solved by repeated application of the standard dynamic programming algorithm in time $O(mnw^2)$. This paper gives an improved data-parallel algorithm, running in time $O(mnw/\gamma/p)$ using vector operations that work on $\gamma$ values in parallel and $p$ processors.

1. Introduction

Dot plots are a standard method for local comparison of two biological sequences introduced by Gibbs/McIntyre [6] and Maizel/Lenk [10]. When creating a dot plot, a substring to substring distance is computed for all pairs of fixed-size windows in the input strings. The result can be visualized by a plot showing a dot for each pair of windows that achieves a distance below a fixed threshold. Commonly, the Hamming distance is used [10,9], since it can be computed very efficiently. However, the Hamming distance is a rather crude measure of string similarity. Using a string edit distance or alignment score (see e.g. [7]) for dot plot filtering can greatly improve the sensitivity of the method. In the context of biological sequence comparison, this idea has been implemented by Ott et al. [12], where a sequential algorithm is given which creates an alignment plot for two strings of lengths $m$ and $n$ using a fixed window length $w$ in time $O(mnw^2)$.

In this paper, we give an improved data-parallel algorithm, running in time $O(mnw/\gamma)$ using vector operations that work on $\gamma$ values in parallel, and show experimental speedups from an implementation using MMX [8]. Furthermore, we demonstrate that the algorithm can be parallelized to run on multiple processors using MPI [14].

* Research supported by the Centre for Discrete Mathematics and Its Applications (DIMAP), University of Warwick, EPSRC award EP/D063191/1. Computational resources were provided by the Centre for Scientific Computing at the University of Warwick.
2. Computing longest common subsequences and string alignments

Let \( x = x_1x_2 \ldots x_m \) and \( y = y_1y_2 \ldots y_n \) be two strings over an alphabet \( \Sigma \) of size \( \sigma \). We distinguish between contiguous subsequences of a string \( x \), which can be obtained by removing zero or more characters from the beginning and/or the end of \( x \), and subsequences, which can be obtained by deleting zero or more characters in any position. The longest common subsequence (LCS) of two strings is the longest string that is a subsequence of both input strings; its length (the LLCS) is a measure for the similarity of the two strings. Substrings of length \( w \) are called \( w \)-windows. For a given \( w \), the length of the LCS of two \( w \)-windows \( x_i \ldots x_{i+w-1} \) and \( y_j \ldots y_{j+w-1} \) will be denoted as \( WLCS(i,j) \). An alignment plot for \( x \) and \( y \) consists of all values \( WLCS(i,j) \) with \( i \in \{1,2,\ldots,m-w\} \), \( j \in \{1,2,\ldots,n-w\} \).

Although the LCS is more accurate than the Hamming score, more general similarity measures are of interest in practice. A standard interpretation of LCS is string alignment [7, p. 209 ff.]. An alignment of strings \( x \) and \( y \) is obtained by putting a subsequence of \( x \) into one-to-one correspondence with a (not necessarily identical) subsequence of \( y \), character by character and respecting the index order. The corresponding pairs of characters, one from \( x \) and the other from \( y \), are said to be aligned. A character not aligned with a character of another string is said to be aligned with a gap in that string. Finding the LCS corresponds to computing a maximum alignment when assigning the scores \( w_e = 1 \), mismatch score \( w_\neq = 0 \) and gap penalty \( w_g = -0.5 \). To compute these alignments, we modify the input strings by adding a new character \$\$ to the alphabet, which we insert before every character in both input strings such that e.g. \( abab \) transforms into \( $a$b$a$b \). For input strings \( x \) and \( y \) of length \( m \) and \( n \), the alignment score \( S(x,y) \) can be retrieved from LLCS of the modified strings \( x' \) and \( y' \) as \( S(x,y) = LLCS(x',y') - 0.5 \cdot (m+n) \). We expect the running time of the seaweed algorithm to increase by a factor of four by this reduction, as both input strings double in size.

Our new algorithms are based on semi-local sequence alignment [15], for which we now give the necessary definitions. Throughout this paper, we will denote the set of integers \( \{i,i+1,\ldots,j\} \) by \( [i:j] \), and the set of odd half-integers \( \{i+\frac{1}{2},i+\frac{3}{2},\ldots,j-\frac{1}{2}\} \) by \( \{i:j\} \). We will further mark odd half-integer variables by a "\( \hat{\cdot} \)" symbol. When indexing a matrix \( M \) by odd-half integer values \( i \) and \( j \), we define that \( M(i,j) = M(\hat{i},\hat{j}) \) with \( i = \hat{i} - 1/2 \) and \( j = \hat{j} - 1/2 \). Therefore, if a matrix has integer indices \( [1:m] \times [1:n] \), it has odd-half integer indices \( [1:m+1] \times [1:n+1] \). We also define the distribution matrix \( D^2 \) of an \( m \times n \) matrix \( D \) as \( D^2(i,j) = \sum D(\hat{i},\hat{j}) \) with \( (\hat{i},\hat{j}) \in [1:m+1] \times [1:n+1] \).

Let the alignment dag (directed acyclic graph) \( G_{x,y} \) for two strings \( x \) and \( y \) be defined by a set of vertices \( v_{i,j} \) with \( i \in [0:m] \) and \( j \in [0:n] \) and edges as
follows. We have horizontal and vertical edges \( v_{i,j-1} \rightarrow v_{i,j} \) and \( v_{i-1,j} \rightarrow v_{i,j} \) of score 0. Further, we introduce diagonal edges \( v_{i-1,j-1} \rightarrow v_{i,j} \) of score 1, which are present only if \( x_i = y_j \). Longest common subsequences of a substring \( x_i x_{i+1} \ldots x_j \) and \( y \) correspond to highest-scoring paths in this graph from \( v_{i-1,0} \) to \( v_{j,m} \). When drawing the alignment dag in the plane, its horizontal and vertical edges partition the plane into rectangular cells each of which, depending on the input strings, may contain a diagonal edge or not. For every pair of characters \( x_i \) and \( y_j \), we define a corresponding cell \( (i - \frac{1}{2}, j - \frac{1}{2}) \). Cells corresponding to a matching pair of characters are called match cells, and cells corresponding to mismatching characters are called mismatch cells.

Solutions to the semi-local LCS problem are given by a highest-score matrix which we define as follows. In a highest-score matrix \( A_{x,y} \), each entry \( A_{x,y}(i,j) \) is defined as the length of the highest-scoring path in \( G_{x,y} \) from \( v_{i-1,0} \) to \( v_{j,m} \). Each entry \( A_{x,y}(i,j) \) with \( 0 < i < j < n \) gives the LLCS of \( x \) and substring \( y_i \ldots y_j \).

Since the values of \( A_{x,y}(i,j) \) for different \( i \) and \( j \) are strongly correlated, it is possible to derive an implicit, space-efficient representation of matrix \( A_{x,y}(i,j) \). This implicit representation of a semi-local highest-score matrix consists of a set of critical points. The critical points of a highest-score matrix \( A \) are defined as the set of odd half-integer pairs \( (i,j) \) such that \( A(i + \frac{1}{2}, j - \frac{1}{2}) + 1 = A(i - \frac{1}{2}, j - \frac{1}{2}) = A(i + \frac{1}{2}, j + \frac{1}{2}) = A(i - \frac{1}{2}, j + \frac{1}{2}) \). Consider a highest-score matrix \( A \). The matrix \( D_A \) with \( D_A(i,j) = 1 \) if \( (i,j) \) is a critical point in \( A \), and \( D_A(i,j) = 0 \) otherwise, is called the implicit highest-score matrix.

Tiskin [15] showed that in order to represent a highest-score matrix for two strings of lengths \( m \) and \( n \), exactly \( m + n \) such critical points are sufficient.

**Theorem 2.1** (see [15] for proof). A highest-score matrix \( A \) can be represented implicitly using only \( O(m+n) \) space by its implicit highest-score matrix \( D_A \), which is a permutation matrix. We have: \( A(i,j) = j - i - D_A^{\Sigma}(i,j) \), where \( D_A^{\Sigma} \) is the distribution matrix of the implicit highest-score matrix \( D_A \).

The set of critical points can be obtained using the seaweed algorithm (by Alves et al. [3], based on Schmidt [13], adapted by Tiskin [15]) which computes critical points by dynamic programming on all prefixes of the input strings. This method is graphically illustrated by tracing seaweeds that start at odd half-integer positions between two adjacent vertices \( v_{0,i-\frac{1}{2}} \) and \( v_{0,i+\frac{1}{2}} \) in the top row of the alignment dag, and end between two adjacent vertices \( v_{m,j-\frac{1}{2}} \) and \( v_{m,j+\frac{1}{2}} \) in the bottom row. Each critical point is computed as the pair of horizontal start and end coordinates of such a seaweed (see Algorithm 1). Two seaweeds enter every cell in the alignment dag, one at the left and one at the top. The seaweeds proceed through the cell either downwards or rightwards. In the cell, the directions of these seaweeds are interchanged either if there is a match \( x_k = y_l \), or if the same pair of seaweeds have already crossed. Otherwise, their directions remain unchanged and the seaweeds cross. By Theorem 2.1, the length of the highest-scoring path in \( G_{x,y} \) from \( v_{i-1,0} \) to \( v_{j,m} \) can be computed by counting the number of seaweeds which both start and end within \( (i : j) \).
3. Data-parallel window-window comparison using seaweeds

The seaweed algorithm can be used to compute the LCS of all pairs of \(w\)-windows simultaneously in time \(O(wn)\) for two strings of respective lengths \(w\) and \(n\) (i.e. one of the strings consists of only one \(w\)-window). By Theorem 2.1, the LCS of \(x\) and any \(w\)-window \(y_i \ldots y_{i+w-1}\) is computed as the number of seaweeds starting and ending within the odd half-integer range \(\{i : i + w\}\). By keeping track of only these seaweeds in a sliding window, our algorithm can compute the LLCS for all \(w\)-windows in a single pass over all columns of cells in the alignment dag. We obtain an improved algorithm for comparing all pairs of \(w\)-windows.

**Theorem 3.1.** Given two strings \(x\) and \(y\) of lengths \(m\) and \(n\), the LLCS for all pairs of \(w\)-windows between \(x\) and \(y\) can be computed in time \(O(mnw)\).

**Proof.** We apply the seaweed algorithm for computing the implicit \((w, 1)\)-restricted highest-score matrices for \(y\) and all substrings of \(x\) that have length \(w\). Each application of the seaweed algorithm therefore runs on a strip of height \(w\) and width \(n\) of the alignment dag corresponding to \(x_i \ldots x_{i+w-1}\) and \(y\). A column of cells in this strip can be processed in time \(O(w)\). In each column \(j\), exactly one new seaweed starts at the top of the alignment dag, and exactly one seaweed ends at the bottom. We track seaweeds ending within \((j - w : j)\). To count the seaweeds that have reached the bottom of the alignment dag, we maintain a priority queue \(B\). In each step, one seaweed reaches the bottom of the alignment dag. Furthermore, in each step, we have to delete at most one seaweed from \(B\).

We use a priority queue of \([\log n]\)-bit integers to represent \(B\). For each seaweed that reaches the bottom, we compute its starting point and add it to the queue. We delete the minimum value from the queue if it is smaller than the starting position of the current \(w\)-window in string \(y\). By using a min-heap [4], both operations can be implemented in \(O(\log w)\). The number \(d\) of seaweeds which start within \((j - w : j)\) is then given by the size of queue \(B\). The LLCS of \(y_{j-w+1} \ldots y_j\) and \(x_i \ldots x_{i+w-1}\) can then be calculated as \(w - d\). In total, we have to process \(n\) columns using time \(O(w)\) in every strip. Overall, \(m - w\) strips exist, therefore we obtain running time \(O(mnw)\). \(\square\)

### Algorithm 1 The Seaweed Algorithm

**input:** Strings \(x\) and \(y\)  
**output:** The critical points for \(x\) against \(y\)  
Initialise \(J[i] = i + m\) for \(i \in (-m, n)\)  
for \(r \in [1, n]\) do  
for \(c \in [1, n]\) do  
\(t \leftarrow J[c] + \frac{r}{2}\)  
if \(x_c = y_r\) or \(t > t\) then  
Swap \(l\) and \(t\)  
end if  
\(J[c] = \frac{r}{2} \leftarrow t\)  
end for  
\(J[n + r - \frac{r}{2}] \leftarrow t\)  
end for  
return the points \(\{(i, J[i]) \mid i \in (-m, n)\text{ with } J[i] \neq -\infty\}\)
While this direct application of the seaweed method gives an asymptotic improvement on the method of computing the LCS independently for every pair of windows by dynamic programming, it is not necessarily more practical. The dynamic programming method can exploit the fact that we are only interested in windows with an alignment score above a given threshold. More importantly, the dynamic programming method allows one to improve performance by introducing a step size $h$, and only comparing $w$-windows starting at positions that are multiples of $h$. We will now show how to improve the practical performance of the algorithm.

Algorithm 1 requires $O(\log(m+n))$ bits to represent the start and endpoints of a single seaweed. We first show that for computing alignment plots with a fixed window length $w$, $O(\log w)$ bits are sufficient for tracing seaweeds, independently of the size of the input strings. To show this, we define the span of a seaweed as the horizontal distance it covers in the alignment dag. A seaweed corresponding to a critical point $(\hat{i}, \hat{j})$ has span $\hat{j} - \hat{i}$. Seaweeds that have a span greater than the window length $w$ are not relevant for computing the alignment plot, since they will not start and end within a single window. Furthermore, we are only interested in values with index pairs $(i, j)$ having $i \mod r = j \mod r = 0$, where $r$ is the constant blowup induced by the alignment score (for the scoring scheme described in the previous section, we have $r = 2$). This is equivalent to computing the semi-local LCS for substrings restricted to length $w$, starting and ending at positions $0 \mod r$.

**Definition 3.2.** Let $A$ be a highest-score matrix. The $(w, r)$-restricted highest-score matrix $A_{w,r}$ is defined as $A_{w,r}(i, j) = A(i, j)$ if $j - i \leq w$ and $i \mod r = j \mod r = 0$, and $A_{w,r}(i, j) = \text{undefined}$ otherwise.

This restriction on the highest-score matrices allows us to reduce the number of critical points we need to store, and also to reduce the number of bits required to represent seaweeds in our computation.

**Proposition 3.3.** To represent a $(w, r)$-restricted highest-score matrix implicitly, we only need to store the critical points $(\hat{i}, \hat{j})$ of the corresponding unrestricted highest score matrix for which $\hat{j} - \hat{i} < w$.

**Proof.** Straightforward from Theorem 2.1 and Definition 3.2. \hfill \Box

**Proposition 3.4.** We can represent a single critical point in a $(w, r)$-restricted highest-score matrix for comparing strings $x$ and $y$ using $O(\log(w/r))$ bits.

**Proof.** We store the seaweeds in a vector $S$ of size $m + n$, where each vector element stores $\lceil \log_2(w/r + 1) \rceil$ bits. For each critical point $(i, j)$, we have one vector element $S(i+1/2) = \min(2^{w/r+1} - 1, (j-i)/r)$. Each vector element stores the span of the seaweed starting at $i$.

It is straightforward to see that we only need $O(\log w)$ bits for a vector element: seaweeds in a $(w, r)$-restricted highest-score matrix become irrelevant once their span is larger than $w$, since these critical points will not affect any LCS for a substring of length $w$ (see Theorem 2.1). In order to reduce the number of bits to $O(\log w/r)$, we use the fact that we only need to answer LCS queries correctly.
if \( i \mod r = j \mod r = 0 \). We therefore do not need to distinguish the individual \( r \) seaweeds starting within \([k : k + r - 1]\) with \( k \mod r = 0 \); once they reach the bottom, we only need to know their starting position within a window of size \( r \). We can therefore divide the distance values by \( r \), which gives the claimed number of required bits.

We now show how to use vector instructions for improving Algorithm 1 to trace multiple seaweeds in parallel. A practical example for vector parallelism are Intel’s MMX instructions [8] for integer vector arithmetic and comparison (it would also be possible to implement our algorithm using floating point vector processing, e.g. using SSE [8]). In our algorithm, we assume that all elements \( V(j) \) in a vector \( V \) are \( v \)-bit values. If an element of a vector has all bits set, then this represents the value of \( +\infty \), having \( INF \equiv 2^v - 1 \). When carrying out the seaweed algorithm on columns of the alignment dag, the result of every comparison in a cell of the column depends on the comparison result from the cell above it. To be able to process multiple cells in parallel, we need to process cells by antidiagonals. We can then use vector operations to implement each step in the the seaweed algorithm, as each cell can be processed only using data computed in the previous step. We need to track seaweeds only if they are within the window of interest. In order to keep the required value of bits per seaweed as small as possible (and hence allow a high degree of vector parallelism), we identify seaweeds by the distance of their starting points to the current column. This distance can be represented using \( v = \lceil \log_2 2w + 1 \rceil \) bits (see Proposition 3.4). When advancing to the next column, we use saturated addition to increment all distances in parallel (i.e. saturated addition of one to vector element \( V(k) \) gives \( V(k) + 1 \) if \( V(k) < 2w \), and \( INF \) otherwise). In each step, we compare the characters corresponding to the cells in the current antidiagonal using vectorised mask generation. Given two vectors \( V \) and \( W \), we generate a mask vector which contains the value \( INF \) at all positions \( k \), where \( V(k) = W(k) \) and zero otherwise. The seaweed behaviour in mismatch cells is implemented by a compare/exchange operation which, given two vectors \( V \) and \( W \), exchanges \( V(k) \) and \( W(k) \) only if \( V(k) > W(k) \). To combine the results from the mismatch cells and the match cells, we require an operation to exchange vector elements conditionally using the mask vector \( M \) generated earlier. Given two vectors \( V \) and \( W \), this operation returns vector elements \( V(k) \) if \( M(k) = INF \), and \( W(k) \) otherwise. All these operations can be vectorized efficiently using MMX. Using these operations, we can implement the seaweed operations from Algorithm 1 by storing all seaweeds on the current antidiagonal in a vector \( V \) if they enter the respective cell from the left, and a vector \( W \) if they enter the respective cell from the top. We use a \( v \)-bit shift operation on vector \( W \) in each step to advance the seaweeds leaving cells at the bottom downwards.

4. Experimental Results

We have implemented the algorithm from the previous sections for allowing its application to actual biological sequences. The implementation uses C++ with Intel MMX assembly code. As input data for our tests, we used different biological sequence data sets and a fixed window size of 100 (the nature of the
sequences does not affect the running time of our algorithm, but may affect the impact of the heuristic speedup employed by the heuristic method we compare the results to. In all experiments, we used a vertical step size of 5, i.e. we only compare every fifth window in the first input to all windows in the other string. Using the scoring scheme as described in Section 2 induces a window size of 200 due to the constant-size blowup of the alignment dag. For comparing the results to existing methods, we implemented an alternative fast method for bit-parallel LCS computation [5] to compute the pairwise alignment scores (“BLCS”) – our 64-bit implementation of this algorithm achieves a speedup of 32 over the standard dynamic programming algorithm for inputs of length 200. Furthermore, we compared our results to the code used in [12] (“Heur”) which uses the standard dynamic programming algorithm [17,11] and a heuristic to speed up computation when a minimum alignment score for a window pair is specified. In the Sea-16, vectors of 16-bit values were used. Using the results from Section 3, we can improve this to use 8-bit values, by computing (200,2)-restricted highest-score matrices. The results of our experiments are shown in Table 1. We see that the seaweed-based algorithm is fastest for all data sets. We also see that the heuristic employed by Heur makes this algorithm more effective than the BLCS method for long sequences. However, we note that it would be possible to adapt BLCS to make use of the same heuristic speedup. Overall, these results show that the seaweed algorithm is highly competitive against the repeated dynamic programming approach, and that particularly the byte vector version (Sea-8) is more than seven times faster than the best existing method.

We further conducted experiments to study the scalability on larger numbers of processors using MPI by distributing the computation of the strips between multiple processors (see Table 1, bottom result sets). We obtained good speedup especially for the large datasets both on small and larger parallel systems. Note that our sample datasets are still rather small. We plan to apply the algorithm to whole-genome comparison, which involves much larger input sequences, and hence better speedup on more processors.

Table 1. Execution times in seconds and speedups

| Data Set  | Mikey (2712×628) | Berti (2712×2305) | Jimmy (15k×97k) | Henry (80k×80k) |
|-----------|------------------|-------------------|-----------------|-----------------|
| **MMX vector speedup on Linux/x86_64/1.83GHz Core2-duo (non-MPI), gcc 4.3.1** |
| Heur      | 5.1 ($\div$ 1.0) | 41.1 ($\div$ 1.0) | 2677 ($\div$ 1.0) | 11708 ($\div$ 1.0) |
| BLCS      | 3.6 ($\div$ 1.4) | 37.3 ($\div$ 1.1) | 3680 ($\div$ 0.7) | 16191 ($\div$ 0.7) |
| Sea-16    | 1.4 ($\div$ 3.6) | 10.8 ($\div$ 3.8) | 1026 ($\div$ 2.6) | 4514 ($\div$ 2.6) |
| Sea-8     | 0.5 ($\div$ 10.2)| 3.8 ($\div$ 10.8) | 368 ($\div$ 7.3)  | 1614 ($\div$ 7.3) |
| **Linux desktop system, Core2-quad 2.66GHz, 64-bit, MPI, gcc 4.3.1** |
| 1 core    | 0.4 ($\div$ 1.0) | 2.9 ($\div$ 1.0)  | 271 ($\div$ 1.0)  | 1199 ($\div$ 1.0) |
| 4 cores   | 0.7 ($\div$ 0.6) | 1.3 ($\div$ 2.2)  | 70 ($\div$ 3.9)   | 307 ($\div$ 3.9)  |
| **IBM HPC Cluster [1], 2× dual-core Xeon 3GHz per node, 64-bit, MPI, gcc 4.1.2** |
| 1 core    | 0.67 ($\div$ 1.0)| 3.1 ($\div$ 1.0)  | 225 ($\div$ 1.0)  | 991 ($\div$ 1.0)  |
| 4 cores   | 0.57 ($\div$ 1.2)| 1.4 ($\div$ 2.2)  | 58 ($\div$ 3.9)   | 251 ($\div$ 3.9)  |
| 16 cores  | 1.26 ($\div$ 0.5)| 1.6 ($\div$ 1.9)  | 20 ($\div$ 11.5)  | 66 ($\div$ 14.9)  |
| 64 cores  | –                | –                 | 11 ($\div$ 20.5)  | 23 ($\div$ 42.4)  |
5. Conclusions and Outlook

In this paper, we present a practical algorithm for local string comparison by edit distance filtered dot plots which uses vector-parallelism and recent algorithmic results to achieve both improved asymptotic cost and performance over applying optimized standard methods. We have further shown results from a coarse-grained parallel implementation of the algorithm, which achieved good speedup on different parallel systems. Further performance could be gained by using SSE [8] or newer vector architectures like Larrabee [2] for implementing our code. A few algorithmic improvements are possible as well. In [16], a tree approach is proposed to avoid recomputing all seaweeds in each strip of height \( w \), which allows to perform the computation in time \( O(mn) \). We are currently investigating a practical variation of this theoretical method which further reduces the dependency on the window size, and may improve the algorithm shown here. Moreover, we believe that it is possible to use a similar heuristic to the one applied in [12] to further improve performance.

References

[1] Centre for Scientific Computing, University of Warwick, http://www.csc.warwick.ac.uk.
[2] M. Abrash. A First Look at the Larrabee New Instructions (LRBni). *Dr. Dobb's Journal*, 2009.
[3] C.E.R. Alves, E.N. Caceres, and S.W. Song. An all-substrings common subsequence algorithm. *Discrete Applied Mathematics*, 156(7):1025–1035, April 2008.
[4] T.H. Cormen, C.E. Leiserson, R.L. Rivest, and C. Stein. *Introduction to Algorithms, Second Edition*. MIT Press/McGraw-Hill Book Company, 2001.
[5] M. Crochemore, C.S. Iliopoulos, Y.J. Pinzon, and J.F. Reid. A fast and practical bit-vector algorithm for the longest common subsequence problem. *Inf. Proc. Lett.*, 80(6):279–285, 2001.
[6] A.J. Gibbs and G.A. McIntyre. The diagram: A method for comparing sequences. its uses with amino acids and nucleotide sequences. *Eur. J. Biochem.*, 16:1–11, 1970.
[7] D. Gusfield. *Algorithms on Strings, Trees, and Sequences*. Cambridge Univ. Press, 1997.
[8] Intel Software Developer’s Manuals, http://www.intel.com/products/processor/manuals, 2009.
[9] J. Krumsieck, R. Arnold, and T. Rattei. Gepard: a rapid and sensitive tool for creating dotplots on genome scale. *Bioinformatics*, 23(8):1026–1028, 2007.
[10] J. V. Maizel and R. P. Lenk. Enhanced graphic matrix analysis of nucleic acid and protein sequences. *Proc. Nat. Academy of Sciences of the USA*, 78(12):7665–7669, 1981.
[11] S. B. Needleman and C. D. Wunsch. A general method applicable to the search of similarities in the amino acid sequence of two proteins. *J. Mol. Biology*, 48:443–453, 1970.
[12] S. Ott, S. Gunawardana, M. Downey, and G. Koentges. Loss-free identification of alignment-conserved CRMs. In preparation, 2009.
[13] J. P. Schmidt. All highest scoring paths in weighted grid graphs and their application to finding all approximate repeats in strings. *SIAM J. Computing*, 27(4):972–992, 1998.
[14] M. Sniir, S. W. Otto, D. W. Walker, J. Dongarra, and S. Huss-Lederman. *MPI: The Complete Reference*. MIT Press, Cambridge, MA, USA, 1995.
[15] A. Tiskin. Semi-local longest common subsequences in subquadratic time. *J. Discrete Algorithms*, 6(4):570–581, 2008.
[16] A. Tiskin. Semi-local string comparison: Algorithmic techniques and applications. *Mathematics in Computer Science*, 1(4):571–603, 2008. See also arXiv: 0707.3619.
[17] R. A. Wagner and M. J. Fischer. The string-to-string correction problem. *J. ACM*, 21(1):168–173, 1974.