Sequence analysis

PatMaN: rapid alignment of short sequences to large databases

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ABSTRACT

Summary: We present a tool suited for searching for many short nucleotide sequences in large databases, allowing for a predefined number of gaps and mismatches. The command-line driven program implements a non-deterministic automata matching algorithm on a keyword tree of the search strings. Both queries with and without ambiguity codes can be searched. Search time is short for perfect matches, and retrieval time rises exponentially with the number of edits allowed.

Availability: The C++ source code for PatMaN is distributed under the GNU General Public License and has been tested on the GNU/Linux operating system. It is available from http://bioinf.eva.mpg.de/patman.

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Supplementary information: Supplementary data are available at Bioinformatics online.

1 INTRODUCTION

There is an increasing need to rapidly and accurately align short sequences to genomic or other biological sequences. Short sequence motifs, including restriction enzyme sites, microarray probe sequences, transcription factor binding motifs and miRNA sequence motifs, are abundant in many areas of molecular biology. Identifying these short sequences is a crucial step in designing experiments and analyzing newly available genomic sequence data.

The most widely used approach for aligning sequences to large databases is the BLAST algorithm (Altschul et al., 1990). Further optimized versions have been presented to speed searches for large numbers of sequences. The BLAST family of algorithms search for good alignments only where short, perfect seed matches between the query and target sequence exist. This heuristic vastly improves the overall speed by restricting the expensive alignment process to regions containing these short exact matches. There is a tradeoff between an extensive search and the speed performance of the algorithm. A search with longer seeds may miss some good alignments that contain mismatches or gaps, while shorter seeds will prolong alignment time. This tradeoff is especially severe for short query sequences because these may not contain a seed match to trigger full alignment, thereby missing good hits.

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† The authors wish it to be known that, in their opinion, the first two authors should be regarded as joint First Authors.
Aho–Corasick algorithm [for a complete discussion see Navarro and Raffinot (2002)]. Figure 1 depicts the resulting data structure for a small input example.

Once the tree is constructed, each sequence in the target database is evaluated base by base and compared to a list of partial matches. Each partial match consists of a node together with the number of mismatches and gaps accumulated. The list is initialized with one element containing the root node of the tree and an edit count of zero. In each iteration of the algorithm, all partial matches are advanced along a perfectly matching outgoing edge. Additional elements are stored for following mismatched edges and for producing all possible gaps, as long as the number of edits remains below the threshold given. If the outgoing edge is a suffix link, the resulting partial match is only included if no mismatch or gap occurred in the part before the suffix. The number of edits needed to align the suffix is stored in the partial match when following a suffix link. Matches are reported when a partial match reaches a leaf node before exceeding the predefined number of allowed edits. The sequence identifier, match coordinates and number of edits are printed.

2.3 Complexity

When ambiguity codes are not interpreted and the query sequences contain no ‘N’ character, the keyword tree can be constructed in $O(N)$ time and requires $O(N)$ space, where $L$ represents the total length of all query sequences (Navarro and Raffinot, 2002). When ambiguity is enabled, both time and space requirements increase exponentially in the number of ambiguity codes used in the patterns.

The time efficiency of the search algorithm is linear in the size of the target database, but depends heavily on the maximum edit distance as well as the average length and number of query sequences. For each additional edit operation, an exponentially increasing number of partial matches must be considered, since neighboring mismatched nodes and all possible gapped alignments are searched along with the perfect matching path through the tree. However, if only perfect matches are searched, the algorithm acts like the Aho–Corasick algorithm, and search time depends solely on the length of the target sequence. Time constraints therefore mean that PatMaN is only suitable for searching short sequences with a limited number of edit operations.

3 RESULTS

We used PatMaN to match 201 807 Affymetrix HGU95-A microarray 25mer probes to the chimpanzee genome (panTro2). The parameters chosen for this evaluation allowed up to one mismatch, but no gaps. The program spent $\sim$2.5 h searching through all chimpanzee chromosomes and found 15.9 million hits (including 14.4 million hits to ALU repeat sequences). A table containing all unique hits to the chimpanzee genome is available on our website. Table 1 summarizes the time measured for conducting searches with different edit distance parameters using the same microarray probes and reads from one lane of the Solexa platform for chimpanzee chromosome 22. The measurement shows the exponential increase in runtime with the maximum allowed edit distance.

4 CONCLUSION

We present a new tool for mapping short sequences to large nucleotide databases. The program does not require target or query database preprocessing and runs rapidly when a search is restricted to small edit distances. While we demonstrate the program’s utility by aligning microarray probes, we anticipate further applications in the near future. In particular, mapping tags generated using next generation resequencing technology will require fast approximate matching to genomes to facilitate large-scale analysis of gene expression.

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Conflict of Interest: none declared.

REFERENCES


Table 1. HGU95-A probes and Bonobo Reads against Chromosome 22

<table>
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<tr>
<th>Dataset</th>
<th>Edits</th>
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<th>Run time</th>
<th>Hits</th>
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<td>2</td>
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<td>14 3 $\times$ 10^9</td>
</tr>
</tbody>
</table>

*Benchmarking was performed on a 2.2 GHz workstation. Independently of the chosen parameters $\sim$260 MB RAM were used. 

*Benchmarking was performed on a 1.8 GHz workstation and 8.6 GB of RAM was used during execution. The dataset contains 2.8 million reads of 36 bp length of genomic sequence from a Bonobo individual sequenced on the Solexa GAII platform.