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LALNVIEW: a graphical viewer for pairwise sequence alignments

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Abstract

LALNVIEW is a graphical program for visualising local alignments between two sequences (protein or nucleic acids). Sequences are represented by coloured rectangles to give an overall picture of their similarities. LALNVIEW can display sequence features (exon, intron, active site, domain, propeptide, etc.) along with the alignment. When using LALNVIEW through our Web servers, sequence features are automatically extracted from database annotations (SWISS-PROT, GenBank, EMBL or HOVERGEN) and displayed with the alignment. LALNVIEW is a useful tool for analysing pairwise sequence alignments and for making the link between sequence homology and what is known about the structure or function of sequences. LALNVIEW executables for UNIX, Macintosh and PC computers are freely available from our server (http://expasy.hcuge.ch/sprot/lalnview.html).

Introduction

The detection of similarities with other sequences is often the first step in the identification of relevant features in a new nucleic acids or protein sequence. Many different programs have been developed to search for similarities between biological sequences. Generally, the results are displayed as a 'sequence alignment' in text format. This textual representation is sufficient to analyse similarities between sequences that can be aligned over their entire length. However, in many cases, it is not possible to display a global alignment, e.g. when comparing sequences sharing only discrete regions of similarity, sequences containing internal repeats, or recombined sequences (e.g. mRNA vs. genomic, alternatively spliced transcripts, etc.). In such cases, it is necessary to use local similarity search algorithms. Such searches produce lists of local alignments that are all the more difficult to analyse as the sequences are longer and the repeats more numerous. Another solution to display similarities between two sequences is to use graphical dot-plots. Dot-plot representation is efficient to give an overall picture of discrete and/or repeated regions of similarity between sequences, and some excellent tools have recently been developed (e.g. Schwartz *et al.*, 1991, Sonnhammer and Durbin, 1995). However, in some cases, a linear representation of local similarities between sequences is clearer and easier to interpret than the bidimensional dot-plot representation.

We present here a new tool intended to give a global picture of local similarities between two aligned sequences: LALNVIEW (Local ALigNment VIEWer). By giving an overall view of the similarities encountered between two sequences, LALNVIEW provides an efficient aid to their interpretation.

System and methods

LALNVIEW was written in ANSI C using the SUIT (Simple User Interface Toolkit) library (Conway, 1992). LALNVIEW runs on UNIX workstations (SUN SPARC, Silicon Graphics, DEC Alpha, IBM RS/6000, HP), Macintosh, PC and compatibles, and requires a colour screen.

Calculation of local alignments

LALNVIEW does not calculate the alignments itself: it uses the output of local alignment programs. LALNVIEW is able to read alignments from three widely used software: LFASTA, LALIGN and SIM. LFASTA uses the FASTA heuristic to find local regions of similarity between two sequences quickly (Pearson and Lipman, 1988). SIM and LALIGN are two different implementations of the rigorous algorithm of Huang and Miller (1991) (LALIGN is distributed by William Pearson along with the FASTA package). The Huang and Miller algorithm guarantees to find the *N*-best local alignments between two sequences. Its main drawback is that it is much slower than LFASTA (> 100-fold slower for the comparison of two sequences of 3000 residues each). If sequences are relatively short (< 1000 residues) or if calculation time is not limiting, then the Huang and Miller algorithm should be preferred to LFASTA.

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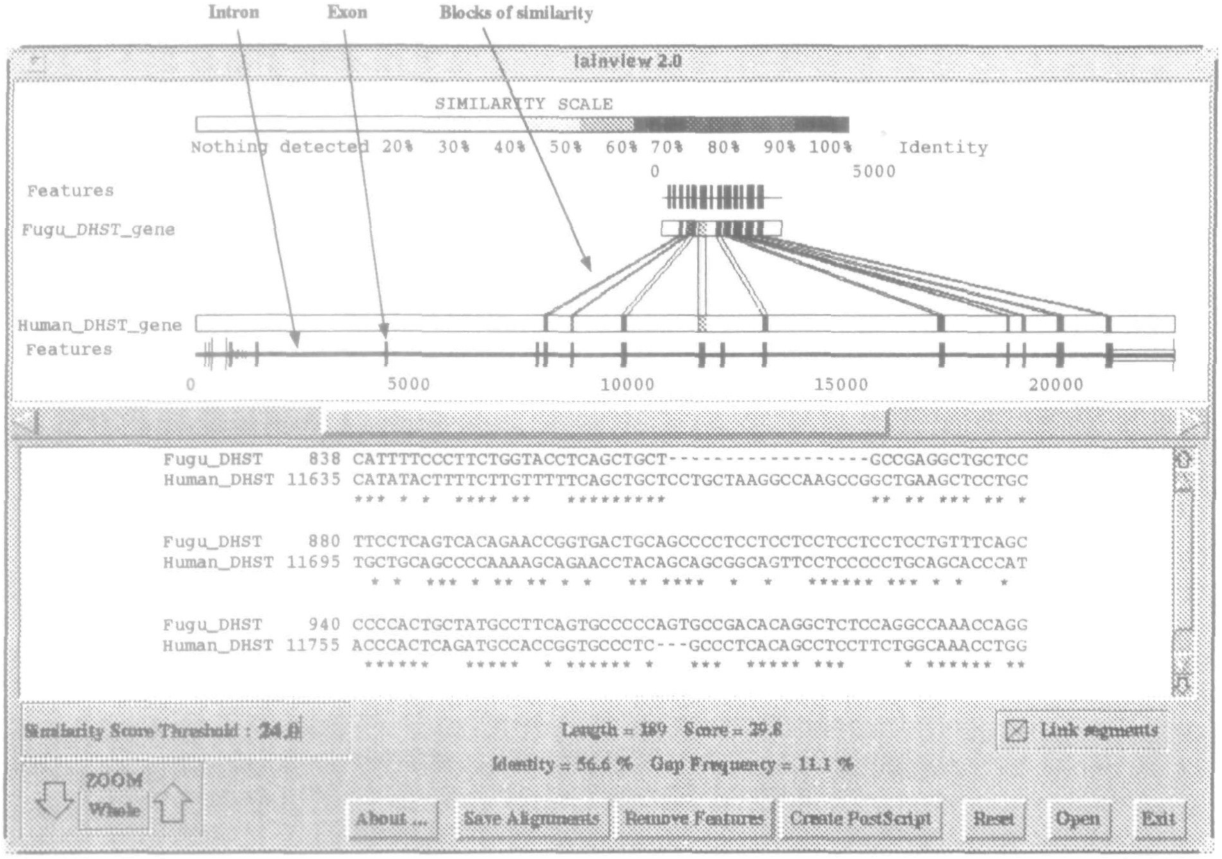

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Fugu_DHST     838 CATTTTCCCTTCTGGTACCTCAGCTGCT------------------GCCGAGGCTGCTCC
Human_DHST  11635 CATATACTTTTCTTGTTTTTCAGCTGCTCCTGCTAAGGCCAAGCCGGCTGAAGCTCCTGC
                  *** * *  **** **   *********                  ** ** *** ** *

Fugu_DHST     880 TTCCTCAGTCACAGAACCGGTGACTGCAGCCCCTCCTCCTCCTCCTCCTCCTGTTTCAGC
Human_DHST  11695 TGCTGCAGCCCCAAAAGCAGAACCTACAGCAGCGGCAGTTCCTCCCCCTGCAGCACCCAT
                   * *  *** * ** ** * *   ** ****  *  *   ****** *** * *   *

Fugu_DHST     940 CCCCACTGCTATGCCTTCAGTGCCCCCAGTGCCGACACAGGCTCTCCAGGCCAAACCAGG
Human_DHST  11755 ACCCACTCAGATGCCACCGGTGCCCTC---GCCCTCACAGCCTCCTTCTGGCAAACCTGG
                   ******   *****  * ****** *   ***  ***** ***     * ****** **
```

Length = 189   Score = 29.8
Identity = 56.6 %   Gap Frequency = 11.1 %

Fig. 1. Comparison of the human dihydrolipoamide succinyltransferase (DHST) gene with its homologue from the fish *F. rubipes* (GenBank accession numbers D26535 and U40758). Genomic sequences were aligned with SIM, using default parameters. Green boxes in the feature lines correspond to protein-coding regions.

Sequence alignment display

Sequences are represented by coloured rectangles to give an overall picture of their similarities. Blocks of similarity between the two sequences are coloured according to the degree of identity between the two segments (Figure 1). LALNVIEW displays all the local alignments with a similarity score greater than a given threshold value. This threshold can be changed by the user to find the best compromise between sensitivity and selectivity and thus increase the signal/noise ratio.

By clicking on a block, the user can align the two sequences according to this anchor point and visualise the corresponding local alignment (textual format) in a second window (Figure 1). A given block (or domain) may be repeated several times in a sequence (Figure 2). Iterative clicking on one block allows the user to successively display all the similar blocks that occur in the other sequence.

Output facilities

The user can save in a text file the alignments that have been considered as significant. He can also save the picture

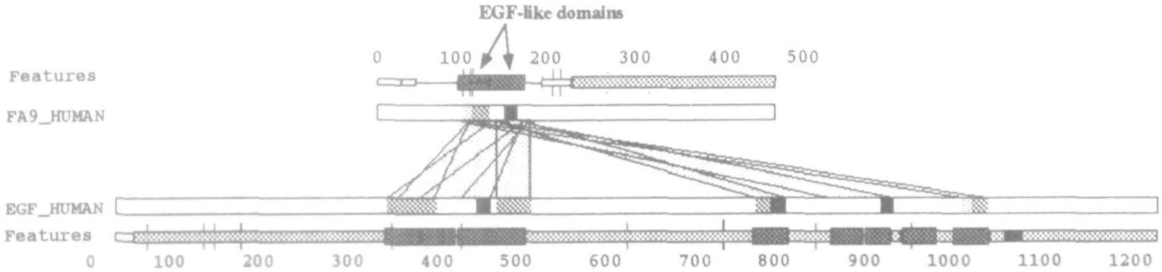

Fig. 2. Comparison of human epidermal growth factor (EFG) and coagulation factor IX proteins (SWISS-PROT accession numbers P01133 and P00740). Protein sequences were aligned with SIM, using the matrix BLOSUM65. Brown boxes in the feature lines correspond to EGF-like domains.

of the sequence alignment as it appears on the screen. It is stored in PostScript format, suitable for printing.

Graphical display of sequence features information

LALNVIEW is also able to display sequence features (active site, domain, motif, propeptide, intron, exon, promoter, etc.) along with the alignment. This option is useful because it allows one to make the link between sequence similarity and what is known about the structure or the function of a sequence. These sequence features are schematically represented by coloured boxes. By clicking on a box, the user can access a short text giving information on this particular sequence (Figure 2).

Using LALNVIEW through the Web

We have implemented SIM on the *ExPASy* Web server (Appel *et al.*, 1994) and LFASTA on the *WWW-Query* Web server (Perrière and Thioulouse, 1996). The pages allowing the use these programs can be accessed at URLs: http:/expasy.hcuge.ch/sprot/sim-prot.html and http://acnuc.univ-lyon1.fr/lfasta.html The user can either provide sequences or accession numbers of sequences from one of the following databases: SWISS-PROT or TREMBL (Bairoch and Apweiler, 1996), GenBank (Benson *et al.*, 1996), EMBL (Rodriguez-Tome *et al.*, 1996) or HOVERGEN (Duret *et al.*, 1994).

Thus the user can compute the alignments on one of these two servers and analyse the results on his local computer with LALNVIEW. The user can declare LALNVIEW as a helper application for his Web Browser (with the MIME type: chemical/x-aln2). This allows the alignment to be automatically displayed with LALNVIEW from the Web Browser.

These Web servers not only provide the alignments, but also sequence features extracted from the annotations available in databases. Automatic extraction of annotations from nucleic sequence databases is not trivial because information relative to one gene can be dispersed in several entries of the database. For example, it is frequent to find genes for which only the exons, but not the introns, have been sequenced. In such cases, each exon corresponds to one entry in the database, but the description of sequence features (protein coding region, transcribed regions, etc.) is given only in one of these entries (generally the one corresponding to the last exon). To solve this problem, we have used the ACNUC sequence database management system (Gouy *et al.*, 1985) that easily handles information relative to sequence structure (location of intron/exon boundaries, of coding regions, etc.) and allows one to retrieve the relationships between sequences corresponding to different parts of the same locus.

Discussion

Figures 1 and 2 give two examples of applications of LALNVIEW. Figure 1 displays the comparison of the human dihydrolipoamide succinyltransferase (DHST) gene with its homologue from the fish *Fugu rubripes*. This figure shows that during the evolution of this gene, only the protein-coding regions, but not the introns, have remained conserved. It also demonstrates that the *Fugu* DHST gene is much more compact than its human homologue, due to shorter introns.

Figure 2 displays the comparison of human epidermial growth factor (EGF) with coagulation factor IX. Regions of similarity between the two proteins correspond to EGF-like domains that are repeated nine and two times, respectively, in EGF and factor IX proteins. In both examples, it is clearly not possible to compute a global alignment between the two sequences, and hence, it is necessary to use a local alignment search software. The two main features of LALNVIEW are: (i) to allow the user to visualise in a single picture all the regions of similarities between the two sequences and to inspect all the local alignments; (ii) to give, along with the alignment, a graphical representation of what is known about the structure of this sequence (positions of exons, introns, regulatory elements, active sites, domains etc.). The advantage of using LALNVIEW through the ExPASy and WWW-Query Web servers is that sequence information is automatically extracted from the annotations available in databases. Thus, when comparing a new sequence to an already known one, LALNVIEW displays all the information necessary for the interpretations of their similarities.

Comparison with existing software

Different programs have been recently developed to display local sequence similarities using dot-plots (e.g. LAD/LAV: Schwartz *et al.*, 1991; DOTTER: Sonnhammer and Durbin, 1995). However, as already mentioned, a linear representation is sometimes preferable to a dot-plot. The Macaw program (Schuler *et al.*, 1991) uses boxes and lines to give a linear representation of sequence similarities. It has the advantage over LALNVIEW to be able to display multiple sequence alignments, and not only pairwise alignments. However, this program is not available for UNIX computers and, unlike LALNVIEW, LAD/LAV or DOTTER, does not allow one to display sequence features. Indeed, the main originality of LALNVIEW is the automatic display of sequence features, as implemented on our Web servers. To ensure that everyone can take advantage of this facility, LALNVIEW is supported for UNIX, Macintosh and PC computers, whereas the programs cited above are available for only one platform.

Availability

LALNVIEW executables are available by anonymous FTP (expasy.hcuge.ch/pub/lalnview), World Wide Web (ftp://expasy.hcuge/ch/pub/lalnview) or by sending an e-mail to duret@dim.hcuge.ch.

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