Sequence analysis

CDvist: a webserver for identification and visualization of conserved domains in protein sequences

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1 Introduction

The identification of protein domains is a key feature of protein sequence analysis. Several databases, notably Pfam (Punta et al., 2012), Simple Modular Architecture Research Tool (SMART) (Letunic et al., 2009), Clusters of Orthologous Groups (COG) (Tatusov et al., 2003), Conserved Domain Database (CDD) (Marchler-Bauer et al., 2013) and others, develop and maintain domain models. Searching tools such as RPS-BLAST (Marchler-Bauer et al., 2013), HMMER3 (Eddy, 2011) and HHpred/HHsearch (Hildebrand et al., 2009; Soding, 2005) are used to match sequences to domain models present in a given database. The size of the protein sequence database grows dramatically, whereas its coverage by pre-computed domain models increases very slowly (Rekapalli et al., 2012). Consequently, sensitive domain searches of sequences in bulk are necessary to improve computational coverage of the current and future protein sequence space. Despite the overwhelming success of the current state-of-the-art domain searching resources, three areas require further improvements: (i) combining tools with high specificity and tools with high sensitivity in a single framework, (ii) multiple query searches using highly sensitive (e.g. profile-to-profile) methods, (iii) visualization of most relevant information in a responsive and interactive way.

To address these issues, we have developed the Comprehensive Domain Visualization Tool (CDvist), a domain-searching webserver specialized in maximizing domain coverage of multidomain protein sequences with emphasis on visualization.

2 Implementation and features

Users submit protein sequences in FASTA format and each sequence is processed independently of each other on individual linux cluster nodes. Up to 500 queries per request are supported. The following...
domain search methods are implemented in CDvist: HMMER3 (Eddy, 2011), RPS-BLAST (Marchler-Bauer et al., 2013; Schaffer et al., 1999), HHSEARCH (Soding, 2005), and HHBLITS-HHSEARCH (Remmert et al., 2012). Transmembrane regions are predicted by either TMHMM (Sonnhammer et al., 1998) or Phobius (Kall et al., 2007). Low complexity and coiled coil regions are predicted by SEG (Wootton, 1994) and Coils (Lupas, 1996) respectively. To improve domain coverage, rather than using the entire sequence, CDvist iteratively identifies regions without significant domain match (orphan segments) and submits each one of them to similarity search against a user-determined sequence of databases until the entire protein sequence is covered or all databases have been searched (Fig. 1). The key principle of this process is that tools that have high specificity—HMMER against Pfam and RPS-BLAST against CDD—are used first. Only then, the sequence segments that were not confidently matched to any model are used to build profiles and subjected to more sensitive profile-profile searches by HHsearch. Each algorithm can be turned on/off and the order of databases, and their significance thresholds, can be altered. This flexibility enables users to tailor the overall process for their specific purposes. Optional ‘domain split’ function splits the matched domain model if there is a considerable unaligned query region (5% by default) in the query-model alignment. This unaligned region is considered as an orphan segment and is used in the next run to search for potential domains.

A custom built JavaScript module powers the visualization on the client side with images in vector format (SVG) that are practical to edit, export as PDF and produce figures of publication quality. Results are displayed asynchronously for each query sequence submitted, which also allows the user to interact with the data before the completion of the entire request. Domain coverage bar provides information on what portion of the matched domain model is represented on the query sequence (Fig. 1f). Alignment quality is represented as vertical bar for each position of the alignment. Gaps in the alignment indicate that the corresponding part of the query is not aligned with the model (Fig. 1g). Scaled sequence information is mapped on the domain architecture, which is easily retrievable by zooming in on the browser. Drag feature allows user to align desired parts of batch data for further analysis. All this information is hosted in our webserver for over a week with a unique URL. Alternatively, the user can retrieve the HTML file to control the interactive feature visualizations locally on a web-browser. JSON formatted files containing the information used to draw the graphics in the website are available not only for each individual sequences but also for the entire input set as a single file. Finally, the log files for each run are available, which display the raw output of the whole process. Logs provide extra information on less significant hits which are not displayed visually. The databases are updated immediately upon their release.

3 Discussion
CDvist is designed to provide maximum domain coverage in protein sequences by bundling the best current domain search tools into a pipeline that exhaustively searches through a series of domain databases in an iterative fashion. This methodology yields the most comprehensive domain architecture for a given protein sequence. Rich visualization, download options and linear speed-up for bulk queries should be appealing to both biologists and bioinformaticians. This webserver would be especially useful for multi-domain proteins with rare or unique domain architectures and those prone to domain swap, where whole sequence similarity searches often yield uninformative and misleading results (Iyer et al., 2001).

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References


