PAST: fast structure-based searching in the PDB
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ABSTRACT
PAST is a new web service providing fast structural queries of the Protein Data Bank. The search engine is based on an adaptation of the generalized suffix tree and relies on a translation- and rotation-invariant representation of the protein backbone. The search procedure is completely independent of the amino acid sequence of the polypeptide chains. The web service works best with, but is not necessarily limited to, shorter fragments such as functional motifs—a task that most other tools do not perform well. Usual query times are in the order of seconds, allowing a truly interactive use. Unlike most established tools, PAST does not prefilter the dataset or exclude parts of the search space based on statistical reasoning. The server is freely available at http://past.in.tum.de/.

INTRODUCTION
As the Protein Data Bank (PDB) (1) today (January 2006) holds >30,000 structures and continues to grow by >100 structures per week, fast and effective methods for identifying similarities between proteins are needed. While proven and efficient methods based on the comparison of the (amino acid) sequence exist, similar tools for the better preserved structural similarities have thus far been lacking. Computationally, searching in large geometrical databases is a difficult problem. With respect to this problem, established approaches ‘fail’ in the following ways:

(i) They try to sidestep the challenge of many geometrical comparisons by prefiltering the candidate set according to various heuristics, e.g. according to amino acid sequence similarity (which can miss matches because of worse sequence conservation versus conservation of structure), or they work only with a small subset of all PDB entries.
(ii) Most existing methods are based on exhaustive search and pairwise comparison, which leads, as a consequence to query times scaling at least linearly with the numbers of structures to be searched. Owing to the nearly exponential growth in number of structures in the PDB, this must be considered unsatisfactory.
(iii) Existing tools are too slow for interactive exploration of the currently existing protein data. A typical search for a protein substructure of interest can take minutes to hours or even days.

We found these shortcomings in the following tools: DALI (1), CE (3), PRIDE (4), VAST (5), SPASM (6), SSM (7), TOPS (8) and YAKUSA (9), among others. We will show that it is possible to perform true interactive searches for identical or similar backbone conformations of protein (sub-)structures. Our approach, PAST (Polypeptide Angle Suffix Tree), first described in Ref. (10), uses a linear representation of the protein backbone conformation which is stored in a suffix tree. Unlike most other search methods, PAST does not have to use a filtered subset of ‘structural representatives’ but includes all polypeptide structures contained in the PDB.

METHODS
Protein structure representation
To describe the 3D conformation of a protein we use the sequence of $\alpha$, the dihedral torsion angle around the virtual bonds between two consecutive $C_{\alpha}$ atoms defined by the four $C_{\alpha}$ atoms $i-1$, $i$, $i+1$ and $i+2$. These torsion angles have the advantage of being invariant to translation and rotation of the protein structure in the actual coordinate system.

The angles are encoded into an alphabet (represented by the characters with ASCII codes from 1 to 36) by discretizing the intervals of size $360^\circ/36 = 10^\circ$. This transforms the information of the 3D backbone conformation from all protein structures contained in the PDB into sequences of ‘structural texts’ which are then stored in the suffix tree data structure. An alternative encoding using the sequence of the backbone dihedral torsion angles $\phi$ and $\psi$ will be added in the near future. (It is already available for the local installation version.)

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Construction of PAST

For the initial construction of the indexing data structure, an extension of Ukkonen’s algorithm (11) to generalized suffix trees (12) is used. For PDB files containing polypeptide structures, all chains, models and alternative location indicators are handled as separate entries and included in PAST. As of January 2006, a total of 32,800 files describing polypeptide structures gives 165,000 separate entries in PAST. The computation of the generalized suffix tree, given the $\alpha$ angle sequences of all polypeptide entries of the PDB, takes $\sim$2–3 min on a standard PC (1 GHz). The size of the suffix tree is $<2$ GB; thus it can be held in main memory, making all calculations extremely fast.

Exact and approximate matching

Exact matching is performed by computing the respective dihedral torsion angles of the query structure, encoding the angles into characters analogously to the database pre-processing step and using the resulting text to perform a suffix tree search. However, in most cases one wants to find not only identical matches but also entries similar to the query structure. Approximate matching is performed by including ‘neighboring’ characters (i.e. neighboring torsion angle intervals) in the search procedure. The worst case query time complexity of the exact search method does not depend on the size of the database. It is bounded by a linear function of query sequence length and the number of occurrences (hits). The approximate search is still very fast in practice because the resulting suffix tree is sparse compared to the angle sequence space, even though its worst case time complexity is much worse in theory (exponential in the length of the search pattern). For a more detailed description of the data structures and algorithms used see Ref. (12).

Post-processing

Post-processing of the results set includes root mean square deviation (r.m.s.d.) calculation of values between $C_\alpha$ atoms of the protein backbone structure from the query and all matching database entries. Despite a quality measure for structural similarity of the hits, the calculated $C_\alpha$ r.m.s.d. value is used as a cutoff for the resulting output.

INTERPRETING THE RESULTS

After submission of a query the results table should be loaded automatically within a short span of time. A screenshot of the results table for the test example is shown in Figure 1b. The results page is structured as follows: on the top of the table the search parameters are given followed by an (unsorted) list of all (sub)structures that match the respective query. For each fragment, the PDB ID, Model, Chain and Alternate Location Indicator (Loc) together with the Position (first and last residues) and the respective amino acid sequence is given. The PDB IDs are linked to the respective PDB entry files. The last column of the table shows the search specific calculation results. The degree values are PAST specific owing to the internal torsion angle representation of the structures.

MaxDiff shows the maximum occurring angle difference between the query and the match.

AvgDiff shows the average angle difference between the query and the match.

r.m.s.d. gives the squared r.m.s.d. values of the angle differences between the query and the match.

$C_\alpha$ r.m.s.d. gives the squared r.m.s.d. values of $C_\alpha$ atom coordinates of the query and matching polypeptide structure in Å.

The $C_\alpha$ r.m.s.d. offers a algorithm/approach independent similarity measure for the found matches. Note that the $C_\alpha$
r.m.s.d. is calculated including all Ca atoms of the query and target segment.

Example query

The following example query uses the CCHC zinc finger motif of the PDB entry 1MFS (residues 15–28). Searching with the α torsion angles by using a tolerance of ±0 coding intervals (exact matching) and a Ca r.m.s.d. cut-off at 2.5 Å only the respective PDB entry itself is found. Raising the tolerance to ±2 leads to 308 matching structures belonging to 15 different PDB entries (data not shown here in detail). All models and calculated averages of a PDB entry are shown as separate matches. With a quick inspection of the results that are using the provided amino acid sequence all entries can easily be identified as members of the respective SCOP (Retrovirus zinc finger-like domain) and PROSITE (PS50158) families. Without Ca r.m.s.d. filtering, the first ‘false positive’ hit (1CJG, MaxDiff 28.8, Ca r.m.s.d. 3.08 Å) occurs using a tolerance of ±3 intervals, which means a total search range of seven coding intervals (i.e. 70 allowed for each position).

CONCLUSION

Our method of discretizing the backbone torsion angles and putting the respective character encoding into a generalized suffix tree has proven to be a very fast solution for answering queries about local structural similarities to the PDB. As the web server implementation of PAST performs an ungapped structural alignment using an overall maximum deviation cut-off, its strength lies in the identification of short polypeptide fragments of local similarity rather than comparing full protein chains. Queries of ~10–50 residues gave good results during the testing phase. Most established tools for structural comparison (except SPASM) either perform badly on such short query structures (SSM, CE, VAST) or even do not even accept them like DALI.

Compared with SPASM, PAST shows comparable or better results, while being much faster. More detailed results are provided in the Supplementary Data and are also given in Ref. (13).

Implemented in the web service PAST, our method, improves on the shortcomings mentioned in the Introduction in the following ways:

(i) Searches are performed including all polypeptide structures contained in the PDB.

(ii) It is based on the data structure of a suffix tree and hence shares an interesting property with it: the search time does not depend on the size of the database, but on the length of the query structure and the number of matches.

(iii) On our web server the usual search time is in the order of seconds, enabling true interactive working by repeated searches. At the same time, the quality of the results is at least comparable to established structural search tools.

Hence, we consider PAST to be a valuable tool for the fast detection of short consecutive protein backbone structures usually found in motifs and domains.

SUPPLEMENTARY DATA

Supplementary Data are available at NAR Online.
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