Structural Bioinformatics - Understanding Protein Structure and Function

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Introduction

Structural Bioinformatics deals with the interface between sequence and structure (e.g., structure prediction, structure-based sequence alignment), that between structure and function (e.g., predicting function on the basis of observed structural similarities), and with the analysis of structural information per se (e.g., fold comparison and database construction). In this talk I will discuss four of our recent and on-going Structural Bioinformatics projects.

- We have assessed and compared the performance of eleven web-based servers for fold-comparison that can be used to find out if a newly determined protein structure displays any similarity to known structures [1].

- We have previously described SPASM [2] and the SPASM server [3] that can be used to answer the question: "does this structural motif (e.g., active site, ligand-binding site, or a strange loop) occur in any other protein structures?". One of the earliest tests of the method was to answer the question: "do left-handed helices occur in natural protein structures?". We found a very significant hit and have therefore undertaken a more detailed investigation. The preliminary results of this study will be presented [4].

- In order to make working with sequences easier for structural biologists (and, hopefully, to make working with structures less daunting to people from the "sequence world"), we have developed a workbench called Indonesia [5]. This program, written in Java, can be used to superimpose structures and derive sequence alignments from that, align sequences from scratch or to a profile derived from a (possibly structure-based) sequence alignment, derive HMMs from such alignments, identify short sequence patterns in them, etc. Sequence alignments can also be imported from a range of other programs, and they can edited, coloured, decorated and printed with the program.

- The Uppsala Electron Density Server, EDS [6], provides access to electron-density maps for more than 10,000 crystal structures in the PDB. In addition to the maps, several validation statistics are provided for every entry. It is hoped that this server will help to increase the appreciation of non-crystallographers for the varying quality (accuracy and precision) of the macromolecular crystal structures available from the PDB [7][8].

References:

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[1] M Novotny, D Madsen & GJ Kleywegt, "Evaluation of protein fold comparison servers", Proteins, 54, 260-270 (2004).
[2] GJ Kleywegt, "Recognition of spatial motifs in protein structures", Journal of Molecular Biology, 285, 1187-1197 (1999).
[3] D Madsen & GJ Kleywegt, "Interactive motif and fold recognition in protein structures", Journal of Applied Crystallography, 35, 137-139 (2002).

[4] M Novotny & GJ Kleywegt, to be published.
[5] D Madsen, P Johansson, N Johansson, S Arent, MR Harris & GJ Kleywegt, to be published.
[6] GJ Kleywegt, MR Harris, JY Zou, TC Taylor, A Wählby & TA Jones, submitted to Acta Crystallographica.
[7] GJ Kleywegt, "Validation of protein crystal structures", Acta Crystallographica, D56, 249-265 (2000).
[8] AM Davis, SJ Teague & GJ Kleywegt, "Applications and limitations of X-ray crystallographic data in structure-based ligand and drug design", Angewandte Chemie International Edition, 42, 2718-2736 (2003).

Links:

- electronic reprints: http://xray.bmc.uu.se/gerard/citation.html
- fold-comparison study: http://xray.bmc.uu.se/~marian/servers
- SPASM server: http://portray.bmc.uu.se/cgi-bin/spasm/scripts/spasm.pl
- Indonesia: http://xray.bmc.uu.se/dennis
- EDS: http://eds.bmc.uu.se/