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Protein Peeling 2: a web server to convert protein structures into series of Protein Units.

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Abbreviated running title: Protein Units.

ABSTRACT

Protein Peeling 2 (PP2) is a web server for the automatic identification of Protein Units (PUs) given the 3D coordinates of a protein. PUs are an intermediate level of protein structure description between protein domains and secondary structures. It is a new tool to better understand and analyze the organization of protein structures. PP2 only uses the matrices of protein contact probabilities and cut the protein structures optimally using Matthews's coefficient correlation. An index assesses the compactness quality of each PU. Results are given both textually and graphically using JMol and PyMol softwares. The server can be accessed from <http://www.ebgm.jussieu.fr/~gelly/index.html>.

INTRODUCTION

Even with no relation with the folding process, folded state is often described in a hierarchical way. The top is frequently associated to domains, i.e. autonomous folding units (1) and the bottom to secondary structures (2,3). In the middle, super - secondary structures are frequently identified. Such descriptions are mainly based on frequency of similar motifs, described at different levels of 3D complexity. Many experiments and recent theory of protein folding suggest that the 3D folded state would dictate the folding process. Yet, only few approaches aim at identifying folding features through the analysis of the folded state. In a pioneer work, Wetlaufer was the first to examine the organization of known structures and suggested that the early stages of three-dimensional structure formation, *i.e.* nucleation, occur independently in separate parts of these molecules (4). He referred to these domains as *Folding Units* (5) and suggested that they could fold independently during the folding process, creating structural modules which are assembled to give the native structure (6). Early analysis were often done manually and on a limited number of proteins (4,7-9). Since then, different strategies have been designed for extracting such folding units. The procedures differed in many aspects, for example the measures and the criteria used. Gō (10) for instance based his description on the C_{α} - C_{α} distance map. Janin and Wodak defined putative compact globular units as units with minimal interface area (11). Rose (12,13) identified a disclosing plane that cut the protein chain into compact continuous segments. Subsequently, Zehfus (14) reported an algorithm, extending earlier work by Zehfus and Rose (15) that identified compact structures, and located discontinuous domains in four globular proteins. Sowdhamini & Blundell's approach was based on C_{α} - C_{α} distances and secondary structures (16). Tsai & Nussinov described a scoring function, based on compactness, hydrophobicity and isolatedness, that estimates the stability of these units (12,17). These

different automatic approaches define a hierarchical organization of the protein in compact units (11,12,16-18). However, only few servers are accessible to the scientific community at this time. Moreover, they mainly focus on the top level of organization, namely, protein domains, for instance Protein Domain Parser (19). DIAL, another web tool, focused on automatic identification of structural compact domains given the 3D coordinates of a protein; it extends the detection of other hierarchical levels of three-dimensional organization of protein structure (20) compared to the previous one.

In the present paper, we propose a new Web-server, called Protein Peeling 2 (PP2), aiming at describing different levels of organization of 3D protein structures, depending on the user choices. PP2 is based on a new methodology, able to decompose the 3D protein structure from secondary structures to domains. The procedure may yield an intermediate level of organization, through what we have named, Protein Unit (PU). A PU is defined as a compact sub-region of the 3D structure corresponding to one sequence fragment, defined by a high number of intra-PU contacts, and, a low number of inter-PU contacts. Protein Peeling works from the C_{α} -contact matrix translated into contact probabilities (21). An optimization procedure, based on the Matthews' coefficient correlation (*MCC*) (22) between contact sub-matrices, defines optimal cutting points that separate generally into 2 or 3 PUs, the region examined. The process is iterated until the compactness of the resulting PUs reaches a given limit, fixed by the user. The PU compactness is quantified by an index *CI* for compaction index. This index is based on a correlation coefficient *R* between the mutual entropy of the contact sub-matrices (23-25). The procedure leads to cut the 3D protein structure into a limited set of PUs. Thus, it defines a series of successive nested partitions; *i.e.* a dendrogram showing the successive splitting of the PUs into sub-PUs.

PEELING SERVER

The web server allows working with one structure (or a structural model). Using default parameters, the user upload the PDB file. The contact matrix is then computed and transformed into a probabilities contact matrix. The procedure performs the splitting of protein structures into Protein Units. The results are shown using different tools: (i) dendrogram showing the successive splitting of the PUs into sub-PUs, (ii) contact matrix of the PUs, (iii) 3D representation of the PUs and (iv) summary of the different PUs.

IMPLEMENTATION

Figure 1 shows the flowchart representation of Protein Peeling 2 (PP2) web server. Interface component is composed of web page (HTML) and Common Gateway Interface (CGI). This interface permits to get the values given by the user (parameters and PDB file) and to transmit them to the perl core instance. The core component is so a perl module that embeds all the information necessary to reach the two other components. The first component is constituted of programs that perform the protein peeling process and compute compactness indexes. The second component consists in different rendering softwares. Thus, R software (26) is used to visualize (i) the hierarchical peeling of the protein structure, (ii) the probabilities contact matrix and (iii) the final splitting of the protein structure with its contents in secondary structures. In the same way, PP2 relies on PyMol (27). The communication between the PP2 core instance and the graphical viewer is based on the generation by the PP2 instance of a script. This component manages the post-rendering of the pictures. The conversion is based on the convert program of the ImageMagick suite (<http://www.imagemagick.org>). We have also added the possibility with a Java Virtual Machine to use JMol software. JMol allows

visualizing the final cutting in PUs in 3D (www.jmol.org). It is possible, using such a design, to trigger the rendering by a mechanism different from CGI, for instance interactively using a command line, and to generate a databank of PUs from a non-redundant databank. Further analyses may be therefore easily carried out.

PEELING SERVER FEATURES

Figure 2 presents snapshots of the different information and results given by PP2 web server.

Data input. PP2 supports only the PDB format.

Adjustable parameters (cf. Figure 2a). PUs are split using the C_{α} -distance matrix translated in terms of probabilities. This version of our web server allows changing the C_{α} -distance threshold and the curvature of the probability function. In the same way, it is also possible to use only the regular secondary structures in the creation of the PUs. Minimal size for secondary structures and PUs can also be changed by the user. To stop the peeling process, the R -value threshold can be modified. Moreover, a pruning of the final dendrogram is proposed. It permits to discard PU that presents a low number of inter-contacts, *i.e.* only pertinent cutting will be done.

Representation of the results. During the submission process, an automatic image, generated with Rasmol (28) and representing the protein structure, is shown. After the protein peeling, each PU is characterized by its position in the protein sequence and is associated for its representation to a fixed color.

At first, a summary of the different parameters used is shown (cf. Figure 2b). A dendrogram representation of the peeling process details the different events (cf. Figure 2c). The contact matrix is also represented and colored according to the PUs (cf. Figure 2d).

We also have added a schematic representation of the results with a description of PUs with their contents in secondary structures and a 3D visualization using JMol applet (<http://jmol.sourceforge.net/>) (cf. Figure 2e). This viewer allows observing the entire colored protein in terms of PUs. The user can easily interact with such a description. A classical static representation done by PyMol software (27) is also produced. The corresponding script may be downloaded locally (cf. Figure 2f). A linear representation of the PUs along the sequence is also given (cf. Figure 2g) with the corresponding colors. The precise position of the different PUs is also given in text form with the corresponding *Compaction Index (CI)*, i.e. the index that quantifies the compactness of the PU (cf. Figure 2h). For clarity, only the last level of cutting is given. However, all the other levels are available, with the corresponding *CI* of each intermediate PU (cf. Figure 2i).

Non-redundant databank. An updated non-redundant databank taken from the Protein DataBank (29) is also available. This non redundant set of proteins structures includes 2,309 elements from crystallographic experiments better than 2 Å of resolution given by PISCES server (30). The proteins share no more than 30% of sequence identity. All these structures have been dissected with the Protein Peeling procedure. Results were stocked in a flat file database and theses pre-cut proteins could be easily accessed through a form or by selecting the protein in the list.

PERSPECTIVES

The PU provides a new view of the protein folded state. It offers an original and rapid way to analyze interesting regions in the structure. PP2 web server allows obtaining the composition in terms of PUs of protein structures. PP2 server is thus a useful tool to examine in an original way, the 3D structure of proteins. The different parameters may be easily controlled and the subsequent PUs graphically analyzed. Results are given both textually and visually. In the

future, we would like to analyze the PUs distribution across protein families (31) and perform prediction from the sequence.

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Conflict of interest statement. None declared.

CAPTIONS

Figure 1. Flowchart of the PP2 web server.

Figure 2. PP2 web server. (a) PP2 interface. (b) Summary of the parameters used. (c) Tree showing the protein peeling process with the different final PUs and their positions. (d) Probability contact matrix with the cutting of the PUs. (e) JMol and (f) PyMol representation of the protein coloured according to PUs colors. (g) Linear representation of the PUs with their secondary structure assignments. (h) Sequence positions of the PUs with their *CI* values. (i) Previous level of protein peeling represented by PyMol software.

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